Platelet Aggregation Inhibitors

Field of the Invention

The present invention relates to pharmaceutical agents and compounds which inhibit platelet aggregation in mammals.

Background of the Invention

Fibrinogen is a glycoprotein present as a normal component of blood plasma. It participates in platelet aggregation and fibrin formation in the blood clotting mechanism.

Platelets are cellular elements found in whole blood which also participate in blood coagulation. Fibrinogen binding to platelets is important to normal platelet function in the blood coagulation mechanism. When a blood vessel receives an injury, the platelets binding to fibrinogen will initiate aggregation and form a thrombus. Interaction of fibrinogen with platelets occurs through a membrane glycoprotein complex, known as gp IIb/IIIa; this is an important feature of the platelet function. Inhibitors of this interaction are useful in modulating platelet thrombus formation.

It is also known that another large glycoprotein named fibronectin, which is a major extracellular matrix protein, interacts with fibrinogen and fibrin, and with other structural molecules such as actin, collagen and proteoglycans. Various relatively large polypeptide fragments in the cell-binding domain of fibronectin have been found to have cell-attachment activity. See U.S. Patents 4,517,686; 4,589,881; and 4,661,111. Certain relatively short peptide fragments from the same molecule were found to promote cell attachment to a substrate when immobilized on the substrate or to inhibit attachment when in a

solubilized or suspended form. See U.S. Patents 4,578,079 and 4,614,517.

In U.S. Patent 4,683,291, inhibition of platelet function is disclosed with synthetic peptides designed to be high affinity antagonists of fibrinogen binding to platelets. U.S. Patent 4,857,508 discloses tetrapeptides having utility as inhibitors of platelet aggregation.

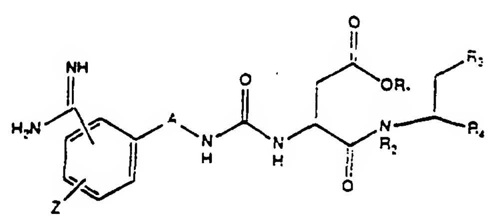
European Patent Application 445,796 discloses platelet aggregation inhibitors which contain peptide linkages, namely N-[N-[4-(p-amidinobenzamido)butyryl]-L-α-aspartyl]valine compounds. The compounds inhibit cell-cell adhesion and the binding of adhesive proteins to platelets.

European Patent Application 372,486 discloses N-acyl beta amino acid derivatives which are useful as cell adhesion inhibitors and are especially useful for inhibiting platelet aggregation.

European Patent Application 381,033 discloses amidino or guanidinoaryl substituted alkanoic acid derivatives which inhibit protein to receptor binding and are useful for the treatment of thrombosis and cardiac infarction.

Summary of the Invention

The present invention relates to a class of compounds represented by the formula:



(I)

or a pharmaceutically acceptable salt thereof

wherein Z is selected from the group consisting of H, halogen, hydroxy, alkoxy of one to six carbon atoms and alkyl of one to six carbon atoms;

wherein A is selected from the group consisting of alkyl of one to six carbon atoms, alkenyl of two to six carbon atoms and alkynyl of two to six carbon atoms;

wherein R_1 is selected from the group consisting of H, alkyl of one to six carbon atoms, aralkyl and alkanoyloxyalkyl;

wherein R_2 is selected from the group consisting of H, alkyl of one to six carbon atoms, and aralkyl optionally substituted on the aryl by hydroxy or methoxy;

wherein R^3 is selected from the group consisting of alkyl, indolyl, pyridyl, benzothiophenyl, phenyl benzofuranyl and furanyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;

wherein R^4 is selected from the group consisting of H, $-COOR_5$ and $-(CH_2)_mCOOR_5$;

wherein m is an integer from 1 to 6; and

wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

It is another object of the invention to provide pharmaceutical compositions comprising compounds of the formula I. Such compounds and compositions have usefulness as modulators and/or inhibitors of platelet aggregation. The invention also relates to a method of therapeutically inhibiting or modulating platelet aggregation in a mammal in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a class of compounds represented by the formula I, described above.

A preferred embodiment of the present invention is a compound of the formula I wherein:

Z is hydrogen;

A is alkyl of one to six carbon atoms;

wherein R_1 is selected from the group consisting of H and alkyl of one to six carbon atoms; and

R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted on the aryl ring by hydroxy or methoxy;

wherein R^3 is indolyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene,

alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;

wherein R^4 is selected from the group consisting of H, $-COOR_5$ and $-(CH_2)_mCOOR_5$;

wherein m is an integer from 1 to 6; and

wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

Another preferred embodiment of the present invention is a compound of the formula I wherein:

Z is hydrogen;

A is alkyl of one to six carbon atoms;

R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms; and

R_2 is selected from the group consisting of H, alkyl of one to six carbon atoms, and aralkyl optionally substituted on the aryl ring by hydroxy or methoxy;

wherein R^3 is pyridyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino,

alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;

wherein R^4 is selected from the group consisting of H, $-COOR_5$ and $-(CH_2)_mCOOR_5$;

wherein m is an integer from 1 to 6; and

wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

Still another preferred embodiment is a compound of the formula I wherein:

Z is hydrogen;

A is alkyl of one to six carbon atoms;

R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms; and

R_2 is selected from the group consisting of H, alkyl of one to six carbon atoms, and aralkyl optionally substituted on the aryl ring with hydroxy or methoxy;

wherein R^3 is phenyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;

wherein R^4 is selected from the group consisting of H, $-COOR_5$ and $-(CH_2)_mCOOR_5$;

wherein m is an integer from 1 to 6; and

wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

Exemplifying these embodiments are the following compounds:

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine.

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-tryptophane

As used herein, the term "alkyl" refers to a straight chain or branched chain hydrocarbon radical having from 1 to 6 carbon atoms. Examples of such alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, hexyl, isohexyl, and the like.

As used herein, the term "alkoxy" includes straight or branched chain lower alkyl ether radicals wherein the term alkyl is as defined above. Examples of such groups are methoxy, ethoxy, n-propoxy, n-butoxy, isobutoxy, t-butoxy, sec-butoxy, isopropoxy and the like.

As used herein the term "halogen" refers to chloro (Cl), fluoro (F), bromo (Br) or iodo (I).

As used herein the term "alkenyl" refers to unsaturated acyclic hydrocarbons containing at least one double bond and 2 to 6 carbon atoms. Examples of such groups are ethenyl, propenyl, butenyl, isobutenyl, pentenyl, hexenyl and the like.

As used herein the term "alkynyl" refers to acyclic hydrocarbons containing one or more triple bonds and 2 to 6 carbon atoms. Examples of such groups are ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

As used herein the term "heteroaryl wherein the heteroatom is N" refers to a radical composed of at least one unsaturated ring wherein one of the carbon atoms is replaced by nitrogen. Examples of such groups are pyridyl, quinolinyl, and the like.

As used herein the term "aralkyl" refers to a radical wherein an aryl group, such as phenyl, naphthyl or pyridyl is attached to an alkyl radical as defined above. Examples of such radicals include benzyl, phenylpropyl, pyridylmethyl and the like.

As used herein the term "aryl" refers to an organic radical derived from an aromatic hydrocarbon by the removal of one atom, such as, phenyl is formed from the removal of one atom from benzene and the like.

As used herein the term "carboxyl derivatives" refer to a radical of the general formula $\overset{\displaystyle O}{\overset{\|}{-C-OR}}$ wherein R is hydrogen or alkyl as defined above.

As used herein the term "alkoxycarbonyl" refers to a radical of the formula $RO-\overset{\displaystyle O}{\overset{\|}{C}}-$ wherein R is an

alkyl group as defined above.

As used herein "alkylamino" refers to a radical of the formula -NHR or -NRR wherein R is an alkyl group as defined above.

The compounds herein as shown in Formula I can exist in various isomeric forms and all such isomeric forms are intended to be included, as well as, pharmaceutically acceptable salts of such compounds and isomers.

In the structures and formulas herein, a bond drawn across a bond of a ring can be to any available atom on the ring.

The term "pharmaceutically acceptable salt" refers to a salt prepared by conventional means. Examples of pharmaceutically acceptable salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, and tartrate salts. (See Berge et al., J Pharm. Sci., 66(1), 1-19 (1977) for additional examples of pharmaceutically acceptable salts.)

This invention also relates to a method of inhibiting platelet aggregation and more specifically, a method of treatment involving the administration of compounds of Formula I to achieve such inhibition.

The platelet aggregation inhibitors of the present invention are useful in the prevention of re-occlusion of an artery following re-canalization procedures such as post-fibrinolytic therapy, thrombolytic therapy, angioplasty and coronary bypass surgery. Other contemplated uses are prevention of recurrent myocardial infarct, unstable angina, peripheral artery disease, cerebral ischemia and shunt procedures.

For the inhibition of platelet aggregation, compounds of the present invention may be administered orally, parenterally, or by inhalation spray, rectally,

or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes, for example, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitonally.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art.

Accordingly, the invention provides a class of novel pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and if desired other active ingredients.

The dosage regimen for treating a condition with the compounds and/or compositions of this invention is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the particular compound employed. Thus the dosage regimen may vary widely. Dosage levels of the order from about 0.01 mg to about 150 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions. The pharmacologically active compounds of this invention can be processed in accordance with conventional methods of galenic

pharmacy to produce medicinal agents for administration to patients, e.g., mammals including humans.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. These may contain, for example, an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose would typically be about 0.01 to 50 mg/kg body weight injected per day in multiple doses depending on the condition being treated.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and

modes of administration are well and widely known in the pharmaceutical art.

The pharmaceutical compositions may be made up in a solid form such as granules, powders or suppositories or in a liquid form such as solutions, suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

The novel platelet aggregation inhibitors of the present invention can be prepared by methods analogous to solution phase peptide synthesis [see: The Peptides: Analysis, Synthesis, Biology (E. Gross and J. Meienhofer, eds.), Vol. 1-5, Academic Press, New York)] combined with standard synthetic method. The general synthetic sequence is outlined in Scheme A. The cyano group is converted to the amidine via the imidate which is formed by treating the benzonitrile with anhydrous hydrochloric acid in ethanol. Treatment of the imidate with ammonium chloride affords the amidine as the salt (HCl). Selective hydrolysis of the ester in the presence of the amidine can be carried out using lithium hydroxide in aqueous methanol. The final compounds for biological testing were obtained by purification by reverse phase high pressure liquid chromatography [High Performance Liquid Chromatography Protein and Peptide Chemistry (F. Lottspeich, A. Henscher, K. P. Hupe, eds.) Walter DeGruyter, New York, 1981].

The benzonitrile urea derivative of Scheme A can be prepared from the corresponding acid derivative using a Curtius rearrangement as outlined in Scheme B. The intermediate isocyanate can be prepared in a three step pr cess using trimethylsilylazide [H.R.

Kricheldorf, Chem. Ber., Vol. 105, 3958-3965 (1972)] followed by aqueous hydrolysis to the amine. The amine is converted to the isocyanate by treatment with triphosghene [H. Eckert and B. Forsten, Angew. Chem. Int. Ed. Engl. 894-895 (1987)] and subsequent reaction with the dipeptide mimetic affords the benzonitrile urea of Scheme A.

Alternatively, the benzonitrile urea is obtained directly from the corresponding acid by treatment with diphenylphosphorylazide [S. Yamada, K. Ninomiya and T. Shioiri Tetrahedron Lett. 2343 (1973); P.A.S. Smith Org. React. Vol. 3, 337 (1946); J.H. Saunders, R.J. Slocombe, Chem. Rev., V. 43, 203 (1948)] followed by trapping the intermediate isocyanate with the dipeptide mimetic.

The benzonitrile acid of Scheme B where A=alkenyl, alkynyl, or alkyl having 2 to 4 carbon atoms can be prepared in the following manner (Scheme C): The halobenzonitrile (Z=H) is coupled to an omega alkynoic (Scheme C-Method 1) or alkenoic acid (Scheme C-Method 2) using a palladium(0) based coupling reaction ["Heck Reaction"- Palladium Reagents in Organic Syntheses (Richard F. Heck), Academic Press, New York, 1985].

The preferred conditions for the palladium coupling reaction differed for the alkynoic acid and the alkenoic acid coupling components. When A=alkynyl having 2 to 4 carbon atoms, the preferred conditions for the palladium coupling reaction utilized tetrakis(triphenylphosphine)-palladium(0) as catalyst and piperidine as the solvent [Scheme C-Method 1, for related conditions see: H. A. Dieck and F. R. Heck J. Organometallic Chem. 259-263(1975)]. When A=alkenyl having 2 to 4 carbon atoms, the preferred conditions for the alkenoic acid coupling component utilized the phase transfer conditions of Jeffery and Larock [Scheme

C-Method 2, T. Jeffery J. Chem. Soc. Chem. Commun. 1287-89(1984); R. C. Larock Tetrahedron Lett. 2603-2606 (1989)]. These conditions [phase transfer agent-tetrabutylammonium salt, catalyst-palladium(II) acetate, base-potassium acetate, solvent-dimethyl formamide] are extremely mild conditions which afforded a good yield of coupled olefin. Compounds where A=alkyl were obtained through a selective reduction of the double bond by catalytic reduction over palladium on calcium carbonate.

The required omega alkenoic acids are either commercially available or can be synthesized by oxidation of the omega alkenols [E.J. Corey and G. Schmidt Tetrahedron Lett. 399 (1979)]. The required omega alkynoic acids are either commercially available or can be synthesized from the omega haloalkanoic acids and lithium acetylide [W.J. DeJarlais, E.A. Emken Synthetic Commun. 653 (1980); J. Cossy, J.P. Pete Tetrahedron Lett. 573 (1986)].

An alternative method for the preparation of the (cyanophenyl)alkenoic acid unit (A=alkenyl) can be employed using a standard Wittig reaction [B.E. Maryanoff, A.B. Reitz Chem Rev. 863-927 (1989)] with cyanobenzaldehyde and an omega substituted (carboxyalkyl)triphenylphosphonium bromide as the two reaction components (Scheme C- Method 3) [for related conditions see: J. Am. Chem. Soc. 397 (1970); *Ibid* 6831 and 7185 (1973)].

The substituents, Z=halogen, alkyl, hydroxy, or alkoxy, can be introduced where A=alkyl at the benzonitrile stage (e.g. compound 4, Scheme F) using bromine, iodine, or chlorine to halogenate the ring (Scheme D). The alkyl group can be introduced by low temperature lithium halogen exchange followed by quenching with the appropriate aldehyde [see: W. E.

Parham, C. K. Bradsher Acct. Chem. Res. 300 (1982)]. The resultant alcohol can be converted to Z=alkyl by hydrogenolysis [Reductions in Organic Chemistry (M. Hudlicky, ed.), John Wiley & Sons, New York, 1984] as shown in Scheme D.

The substituents, Z=hydroxy or alkoxy, can be introduced by low temperature lithium halogen exchange followed by quenching with the electrophilic bis(trimethylsilyl)peroxide [$(TMSO)_2$-Scheme D) M. Taddei and A. Ricci Synthesis 633-635 (1986)] which affords the silyl ether. The silyl ether can be converted to the Z=OH by treatment with hydrochloric acid [M. Taddei and A. Ricci *ibid*]. The Z=OR can be formed by treating the derivative where Z=OH with weak base (K_2CO_3) and an appropriate alkyl halide [R8-Hal, 2 equivalents, see: C.F.H. Allen and J. W. Gates, Jr. Organic Syntheses Coll. Vol. 3 140 (1955)] which will form the ester as well. The ester can be selectively cleaved in the presence of the ether with one equivalent of sodium hydroxide (Scheme D).

Compounds, where R_2 = alkyl, phenyl or phenylalkyl can be prepared by condensation of the appropriate secondary amine with aspartic acid which can be purchased or readily synthesized through a Michael reaction [Advanced Organic Chemistry (J. March, ed.), John Wiley & Sons, New York, 1985] of a primary amine and tert-butyl acrylate or reductive amination [Reductions in Organic Chemistry (M. Hudlicky, ed.), John Wiley & Sons, New York, 1984] processes using the appropriate primary amine and aldehyde.

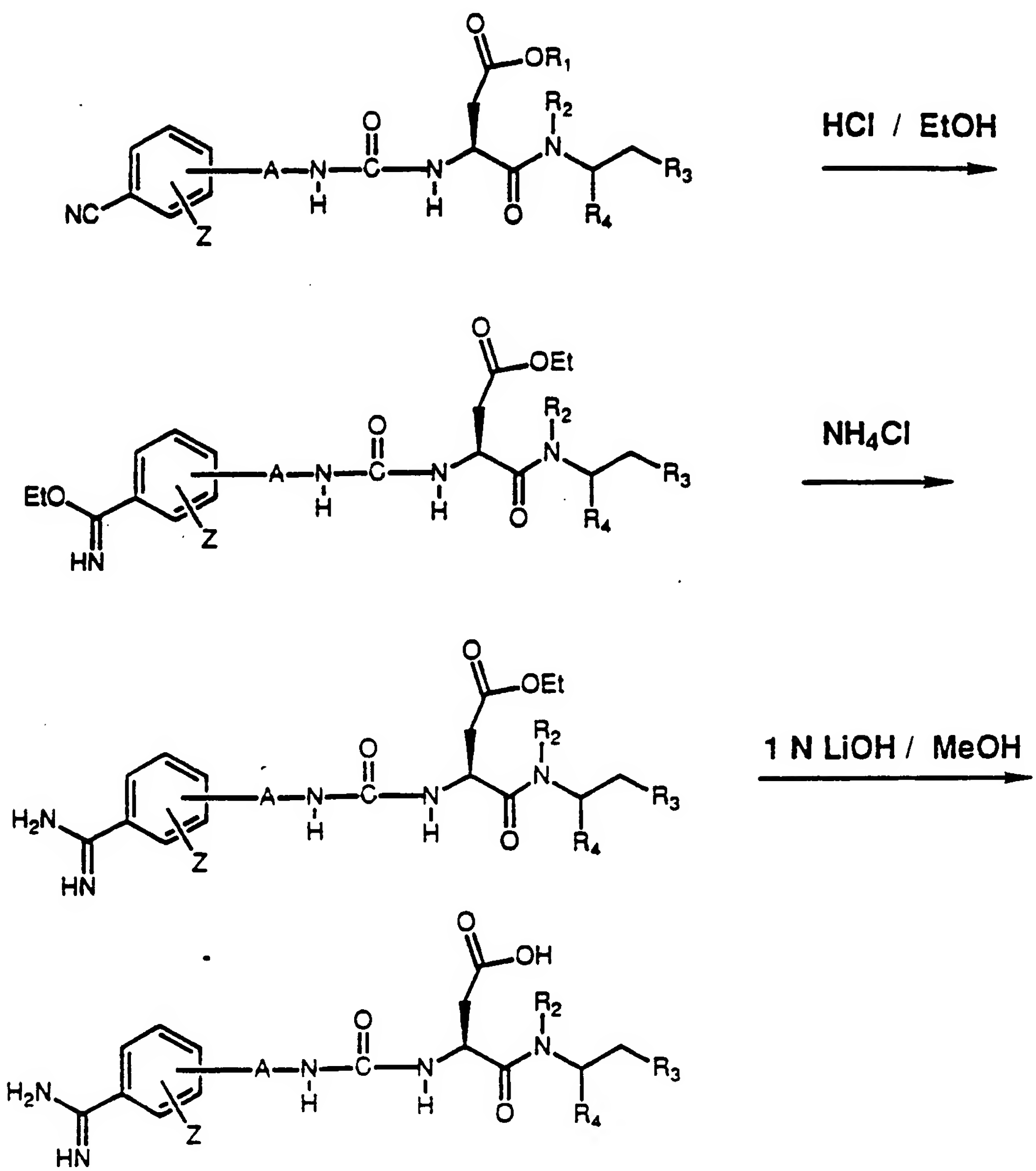
The amino acid containing R_2, R_3, and R_4 is either commercially available or readily synthesized from the available aldehyde as illustrated in Scheme E. Homologation of the aldehyde using a Wittig reaction [B.E. Marynoff and A.B. Reitz, Chem. Rev., 863-927

(1989)] followed by a Strecker amino acid synthesis [Principles of Organic Synthesis (R.O.C. Norman, ed.), John Wiley & Sons, New York, 1978] affords the amino acid as illustrated in Scheme E.

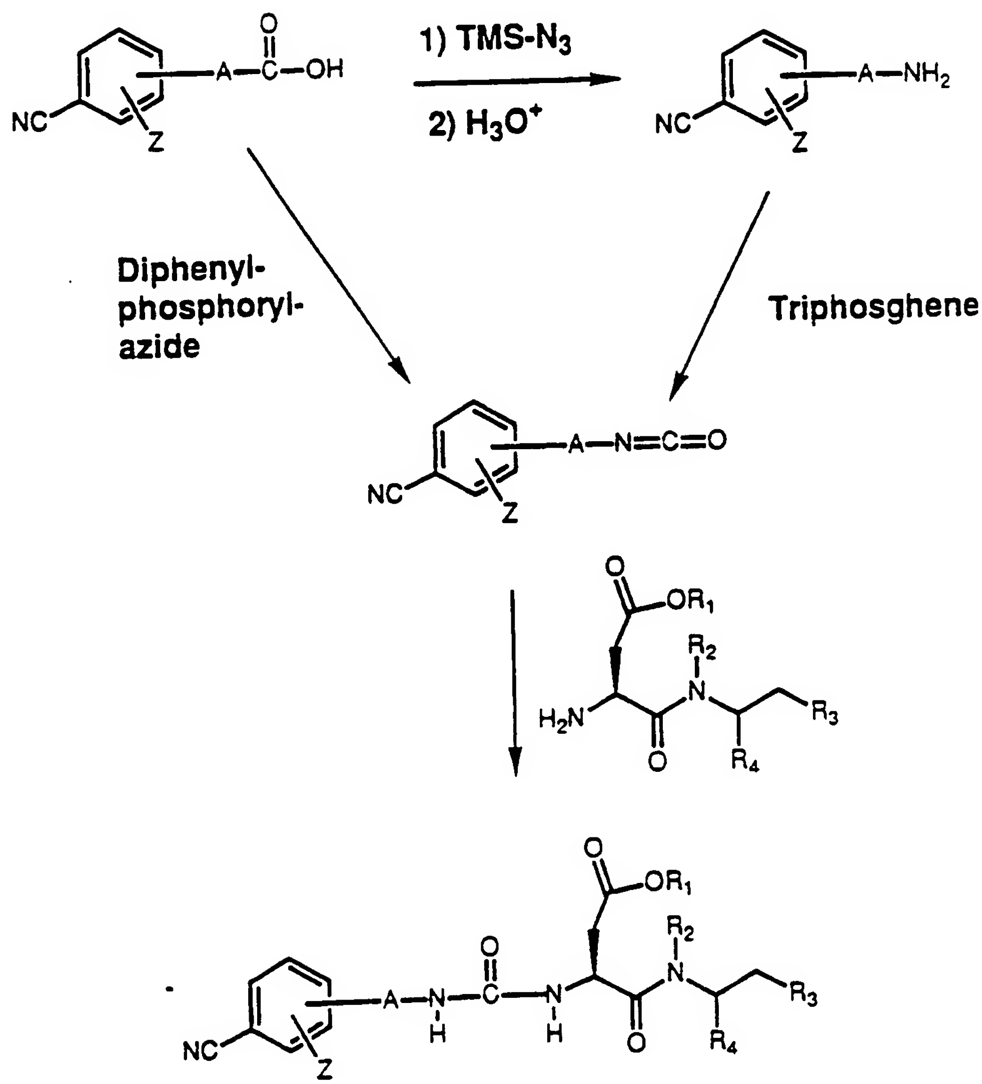
Compounds where R_4 = alkyl carboxyl can be prepared by homologation of commercially available amino acids using the Arndt-Eistert reaction [Meir and Zeller Angw. Chem. Int. Ed. Eng. 32-43 (1975); M. Rodriguez et al Tetrahedron Lett. 5153 (1990); W.J. Greenlee J. Med. Chem. 434 (1985) and references therein] or utilizing other known syntheses of homologated amino acids [e.g. phenylalanine is homologated through the addition of a malonate anion to an activated aziridine obtained from phenylalanine - Tseng, C.C., Terashima, S. and Yamada, S.I. Chem. Pharm. Bull. 29-40 (1977)].

A specific synthesis of antiplatelet agent 10 N-[N-[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]-carbonyl]-L-α-aspartyl]-L-phenylalanine. is shown in Scheme F. The compound numbers used in Scheme F correspond to the compound numbers in Examples 1 and 2. Example 3 was prepared using the method of Examples 1 and 2 with the specific change as stated, and in the general manner described in Scheme A.

Scheme A

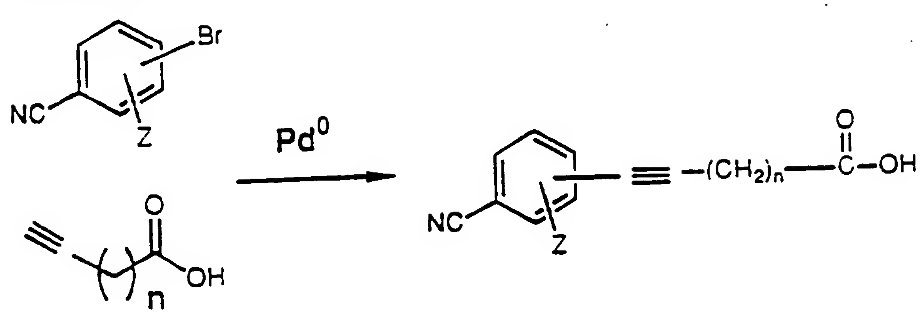

OR1
R2
NC
Z
A
N
H
C
O
R3
R4
HCl / EtOH
OEt
EtO
HN
NH4Cl
H2N
1 N LiOH / MeOH
OH

Scheme B

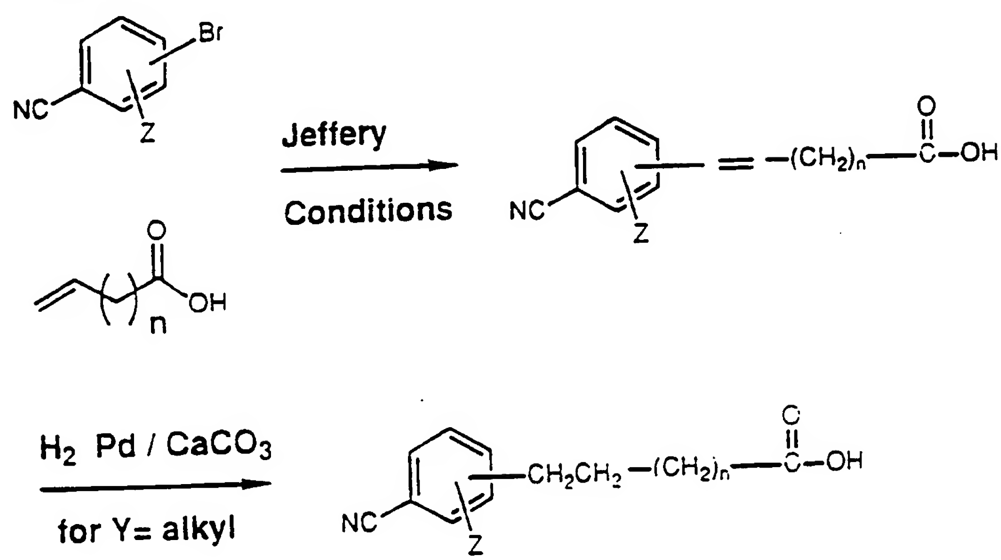

O
A—C—OH
NC
Z
1) TMS-N3
2) H3O+
A—NH2
NC
Z
Diphenyl-
phosphoryl-
azide
Triphosghene
A—N=C=O
NC
Z
OR1
R2
H2N
N
R3
O
R4
A—N—C—N
H
H
NC
Z

SCHEME C

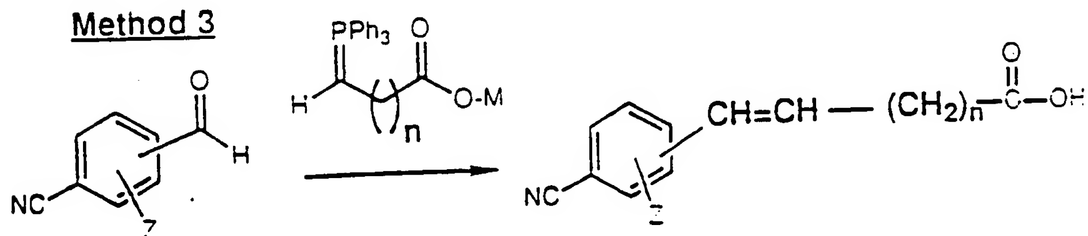
Method 1



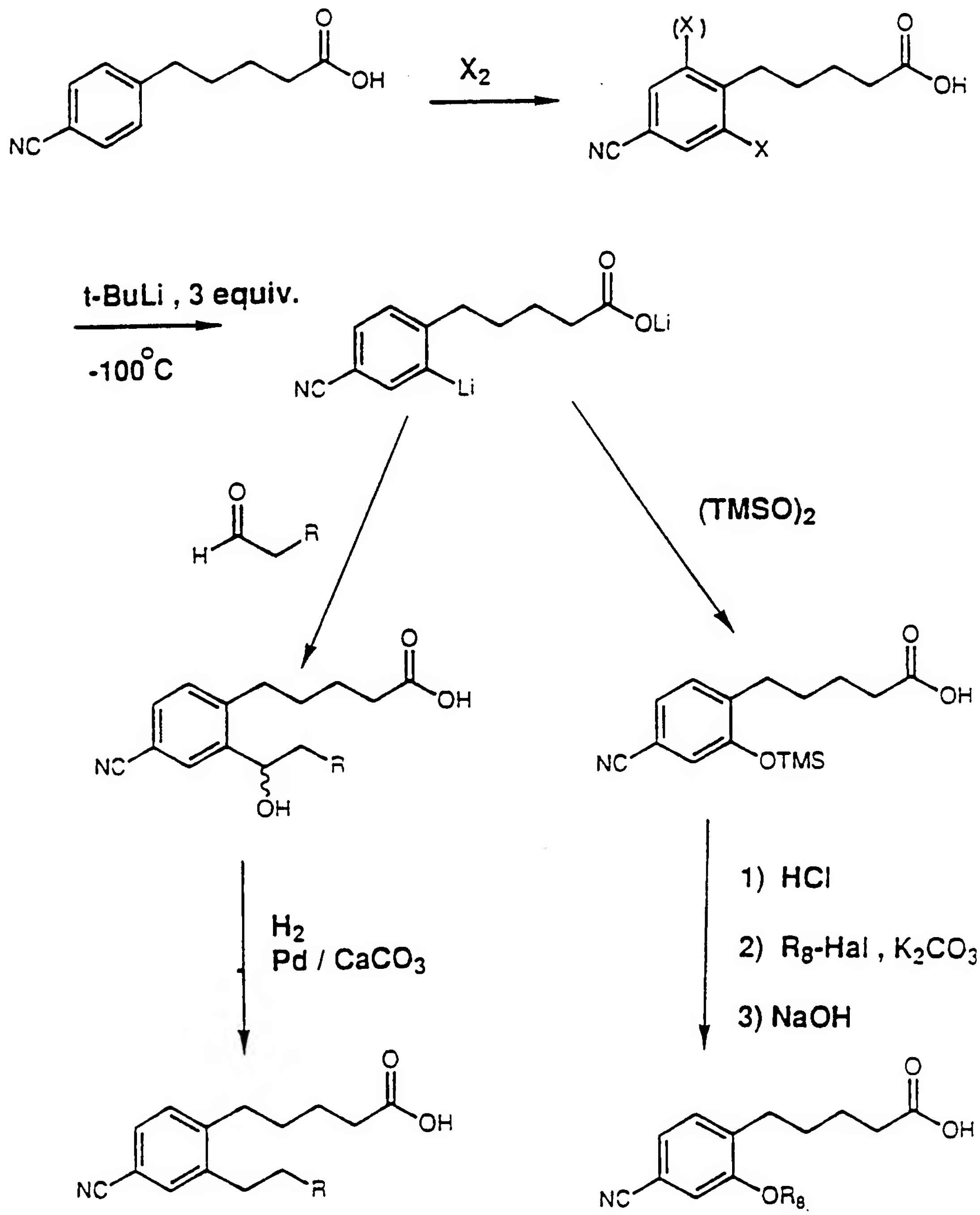
Method 2



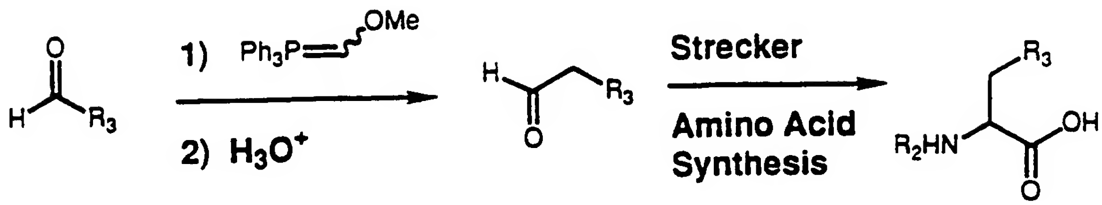
Method 3



Scheme D

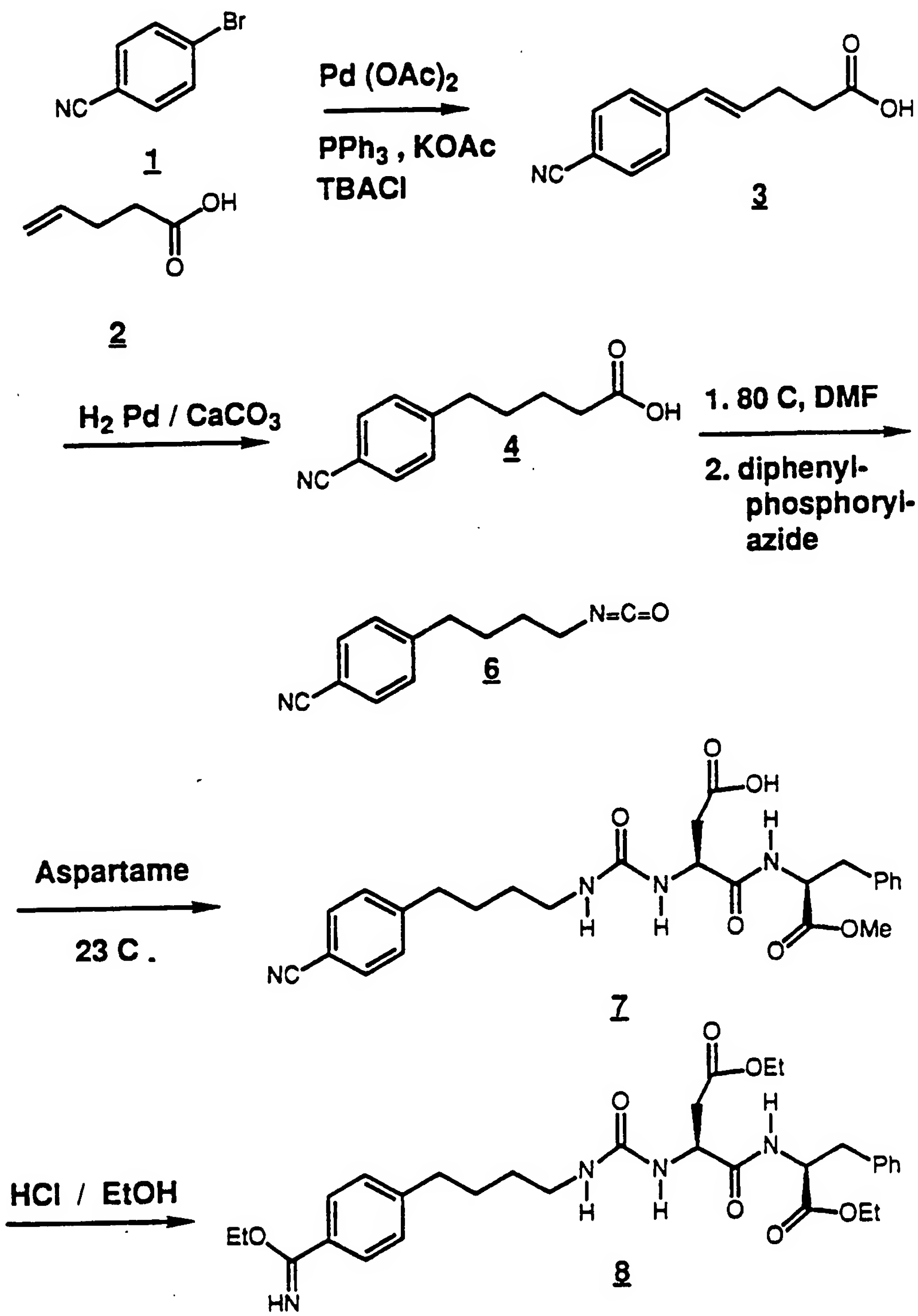

OH
X_2
(X)
X
NC
t-BuLi , 3 equiv.
-100°C
OLi
Li
(TMSO)$_2$
H
R
OTMS
H_2
Pd / $CaCO_3$
1) HCl
2) R_8-Hal , K_2CO_3
3) NaOH
OR_8

SCHEME E

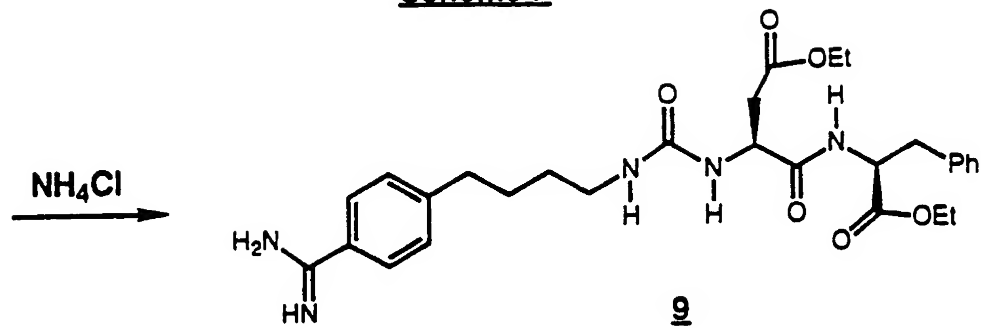


O
H
R_3
1) Ph_3P=
OMe
2) H_3O^+
H
R_3
O
Strecker
Amino Acid
Synthesis
R_3
R_2HN
OH
O

Scheme F


Br
NC
1
OH
O
2
Pd (OAc)2
PPh3 , KOAc
TBACl
O
OH
NC
3
H2 Pd / CaCO3
O
OH
NC
4
1. 80 C, DMF
2. diphenyl-
phosphoryl-
azide
N=C=O
NC
6
Aspartame
23 C .
O
OH
O
H
N
Ph
N
H
N
H
O
O
OMe
NC
7
HCl / EtOH
O
OEt
O
H
N
Ph
N
H
N
H
O
O
OEt
EtO
HN
8

Scheme F



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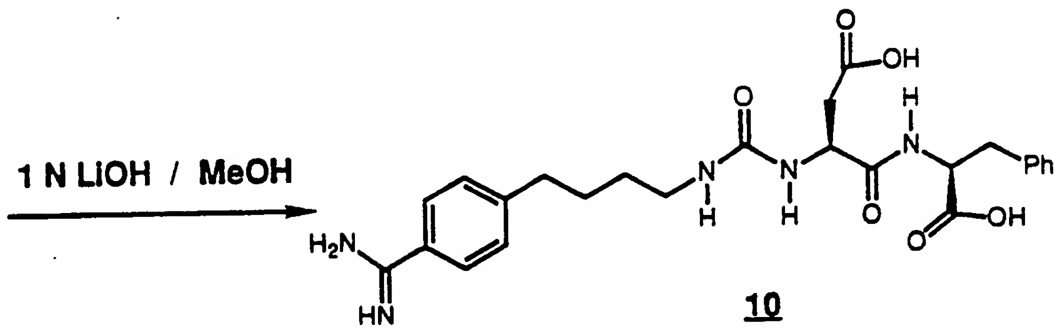

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Contemplated equivalents of the platelet aggregation inhibitors, derivatives and intermediates of the formulas set forth above include compounds having the same general properties, wherein one or more of the various R groups are simple variations of the substituents as defined herein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent can be a hydrogen, a substituent other than hydrogen can be introduced at that position, e.g., a hydrocarbon radical or a halogen, hydroxy, amino and the like, as long as the overall activity and/or synthesis procedure is not affected.

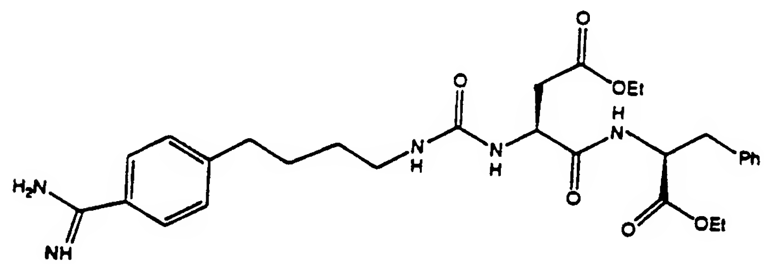
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional.

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of the present invention.

Example 1

Preparation of

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester



Section A.

5-(p-Cyanophenyl)-4-pentenoic acid (3)

Tetrabutylammonium chloride (hydrate, 17.8 g) was dried by azeotroping with benzene (250 mL round bottom flask equipped with a Dean-Stark apparatus). The benzene was removed in vacuo affording anhydrous tetrabutylammonium chloride (17.0 g, 61.2 mmol). To this flask under argon were added triphenylphosphine (820 mg, 3.13 mmol), palladium acetate (703 mg, 3.13 mmol), 4-bromobenzonitrile (16.9 g, 92.8 mmol), potassium acetate (36.8 g, 375 mmol) and 100 mL of degassed anhydrous dimethylformamide (degassed by bubbling argon through for 10 min, dried over molecular sieves). A solution of 4-pentenoic acid (6.27 g, 62.6 mmol) and degassed anhydrous DMF (35 mL) was then added to the rapidly stirring reaction mixture at 23°C.

After 21 hours at 23°C, the reaction mixture was poured slowly into a sodium carbonate solution (3%, 400 mL) and extracted with ethyl acetate (500 mL). The aqueous layer was treated with decolorizing carbon, and filtered. Then, the aqueous layer was acidified to a pH of 2 with 10% HCl which afforded a white solid (6.82 g, 54%): m.p. 150-167°C.

The above procedure affords (3) in sufficient purity to take on to the next step without complications. An analytical sample was obtained by submitting the sample to further purification by flash chromatography (ethyl acetate:methylene chloride:acetic acid, 1:4:0.05) and recrystallization from ethyl acetate (2 times): m.p. 154-156°C.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.50; H, 5.54; N, 6.80.

Section B

5-(p-Cyanophenyl)pentanoic acid (4)

A solution of 1.47 g (7.32 mmol) of (3) in 90 mL of methanol was hydrogenated over 200 mg of 5% $Pd/CaCO_3$ at 5 psi hydrogen over a 1.2 hour period. After removing the catalyst by filtration and evaporation of the solvent *in vacuo*, the residue was triturated with ether followed by hexane which afforded a white solid: m.p. 101-102°C.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.71; H, 6.56; N, 6.87.

Section C.

N-[N-[[[4-(4-cyanophenyl)butyl]aminocarbonyl]-L-α-aspartyl(O-methyl)]-L-phenylalanine

5-(4-cyanophenyl)pentanoic acid (1.01 g; 5 mmol) was dissolved in DMF (30 ml). Diphenylphosphorylazide (1.4 ml; 6 mmol) and N,N-diisopropylethylamine (1.7 ml; 10 mmol) were added slowly with stirring and the solution was heated up to 90°C. After 1 hour, additional diphenylphosphorylazide (0.25 ml) and N,N-diisopropyl-ethylamine (0.5 ml) were added and the reaction continued until the 5-(4-cyanophenylpentanoic acid disappeared on HPLC. The solution was cooled and Asp-Phe-OMe (1.76 g; 6 mmol) dissolved in DMF (10 ml) was added. The mixture was stirred at room temperature for another 3 hours and taken down to dryness on rotavapor to afford crude 7. The oil residue was used without any further purification (FAB-MS: MH+ = 495).

Section D

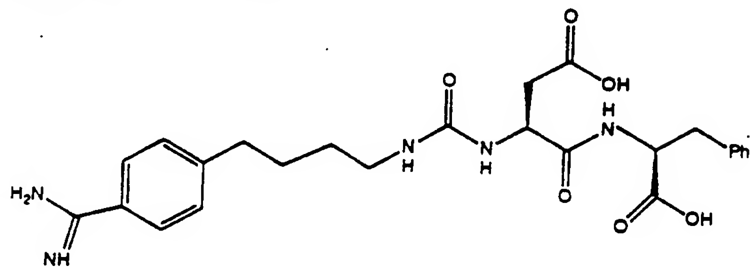
N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]-amino]carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester

N-[N-[[[4-(4-cyanophenyl)butyl]amino]carbonyl]-L-α-aspartyl(O-methyl)]-L-phenylalanine was treated with HCl gas/ethanol (100 ml) in an ice bath for 1 hour. The reaction mixture was then stirred at room temperature over night. The solvent was removed on rotavapor and the residue was dissolved in ethanol (50 ml). Ammonium chloride (0.5 g) and ammonium hydroxide (3 ml in 10 ml H_2O) were added with vigorous stirring. The reaction mixture was gently refluxed overnight and taken down to dryness on rotavapor. The residue was

purified on a HPLC Column as described above. A linear gradient of 10 to 40% acetonitrile/water/0.5% TFA over 30 min. and 40 to 60% acetonitrile/water/0.5% TFA over 5 min. was used. The desired peak was collected and lyophilized to yield 100 mg of 9 as a white solid (FAB-MS; MH+ = 554).

Example 2

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]-carbonyl]-L-α-aspartyl]-L-phenylalanine



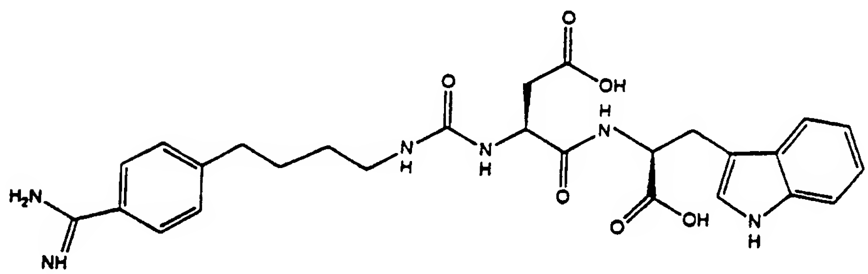
N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]-carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester 9 (100 mg; 1.8 mmol), methanol (25 ml and 1 N LiOH (25 ml) were stirred for 2 hours. Methanol was then removed on a rotary evaporator. The residue was dissolved in 20% acetic acid and purified by HPLC. A gradient of 10 to 40% acetonitrile/water/0.05% TFA over 30 minutes was used. The desired peak was collected and lyophilized to yield 10 as a white solid (60 mg).

Fast Atom Bombardment Mass Spectrometry (MH+) 498
Anal. Calcd. for $C_{25}H_{31}N_5O_6$ plus CF_3CO_2H and H_2O: C,51.51; H,5.40; N,11.12. Found: C,51.40; H,4.84; N,10.98.

Example 3

Preparation of

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]-amino]carbonyl]-L-α-aspartyl]-L-tryptophane

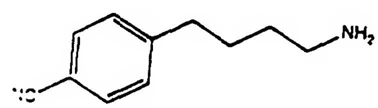


The title compound was prepared in the manner of Example 1 with the following substitution: L-α-aspartyl-L-tryptophane was substituted for L-α-aspartyl-L-phenylalanine in Section C. Fast Atom Bombardment Mass Spectrometry (MH^+) = 537.

Example 4

Preparation of

4-(p-cyanophenyl)butylamine



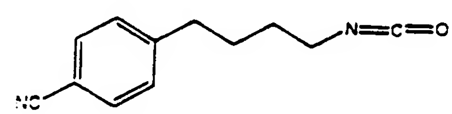
Oxalyl chloride (43.0 mL, 0.492 mol) was added dropwise to a suspension of 5-(p-cyanophenyl)pentanoic acid in 100 mL of dry 1,2-dichloroethane at 23°C under a nitrogen atmosphere. After 5 min, 50 mL of DMF was added. After 30 min, the reaction was concentrated in vacuo. The residue was dissolved in anhydrous THF (150 mL) under a nitrogen atmosphere. Azidotrimethylsilane (14.6 mL, 0.110 mL) was added dropwise at 23°C. After 5 min, the reaction was warmed to achieve reflux for 1 hour. The reaction was cooled to 10°C and concentrated HCl (20 mL) was added over 1 min. The cooling bath was removed and stirring was continued for 15 min. The reaction was concentrated in vacuo and the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was made basic with 1 N NaOH (250 mL) and extracted with ethyl acetate (2 x 200 mL). The organic layer was washed with water (100 mL) followed by brine (100 mL), and dried (Na_2SO_4). After concentration in vacuo, the residue was diluted with ethyl acetate; methanol (150 mL:5 mL) and treated with anhydrous HCl in dioxane (6.9 N) at 0°C. The resultant precipitate was filtered, washed with ethyl acetate then ether. The solid was dried (atmospheric pressure; 55°C) to afford 14.3 g: m.p. 155-160°C.

Anal. Calcd. for $C_{11}H_{15}N_2Cl$: C,62.70; H,7.18; N,13.30.
Found: C,62.76; H,7.35; N,13.34.

Example 5

Preparation of

4-[4-cyanophenyl)]butylisocyanate

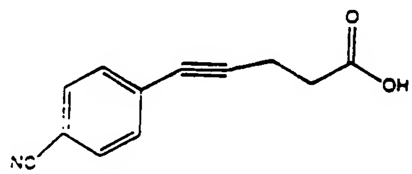


A solution of amine hydrochloride 5 (1.00 g, 4.74 mmol), triphosghene (0.469 g, 1.58 mmol), triethylamine (1.27 g, 12.6 mmol), and dioxane (20 mL) was warmed to 70°C for 2 hours under an argon atmosphere. After cooling to 23°C, the reaction mixture was diluted with ethyl acetate (80 mL), filtered, and concentrated under a stream of nitrogen in the hood to afford the intermediate isocyanate.

Example 6

Preparation of

5-(p-cyanophenyl)-4-pentynoic acid



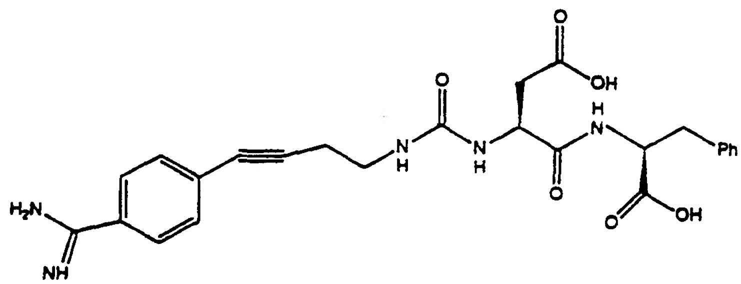
A solution of 4-pentynoic acid (2.15 g, 22 mmol), 4-bromobenzonitrile (3.64 g, 20 mmol), and piperidine (40 mL) was degassed by bubbling nitrogen through the solution for 5 min. prior to the addition of tetrakis(triphenylphosphine)palladium(0) (240 mg, 0.2 mmol). The reaction vial was sealed and warmed to 80°C for 1.5 hours. After cooling to 23°C, the reaction mixture was diluted with ethyl acetate (200 mL), filtered, and concentrated *in vacuo*. The residue was diluted with ethyl acetate (300 mL), washed with 5% HCl (2 x 100 mL), washed with water (1 x 100 mL), and extracted with 3% sodium carbonate (2 x 200 mL). The basic aqueous layer was treated with decolorizing carbon, filtered, and acidified to pH=2. The resultant solid was filtered, washed with water, dried, and purified by flash chromatography (gradient ethyl acetate:methylene chloride:acetic acid 1:9:0.005) and fractional recrystallization (methylene chloride-ether) to afford 5-(p-cyanophenyl)-4-pentynoic acid as a white solid: m.p. 149-152°C.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03.
Found: C, 72.05; H, 4.57; N, 6.94.

Example 7

Preparation of

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]-4-butynyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine

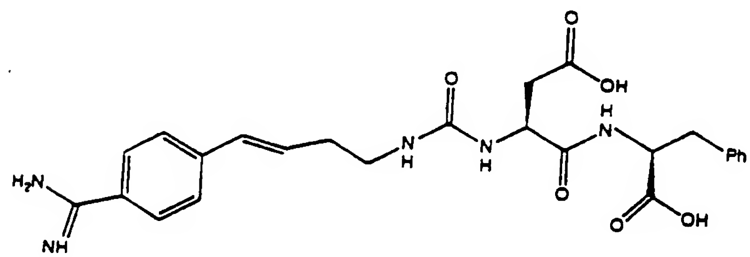


The title compound can be prepared in the manner of Example 1 with the following modification: the 5-(p-cyanophenyl)-4-pentynoic acid is substituted for 5-(p-cyanophenyl)pentanoic acid in Section C of Example 1. The product is purified by reverse phase HPLC using the conditions of Example 1 to afford the title compound. The product is verified by C NMR and Chemical Ionization Mass Spectrometry.

Example 8

Preparation of

N-[N-[[[4-[4-(aminoiminomethyl)phenyl]-4-butenyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine

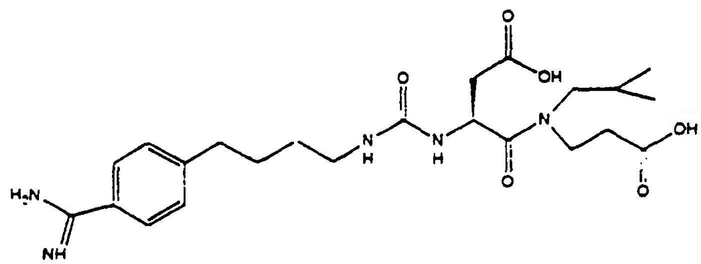


The title compound can be prepared in the manner of Example 1, but the reduction step is omitted (Section B). The product is purified by reverse phase HPLC using the conditions of Example 1 to afford the title compound. The product is verified by C NMR and Chemical Ionization Mass Spectrometry.

Example 9

Preparation of

3S β-[[[[4-[4-(aminoiminomethyl)phenyl]-butyl]amino]carbonyl]amino]-4-[(2-carboxyethyl)(2-methylpropyl)amino]-4-oxobutanoic acid

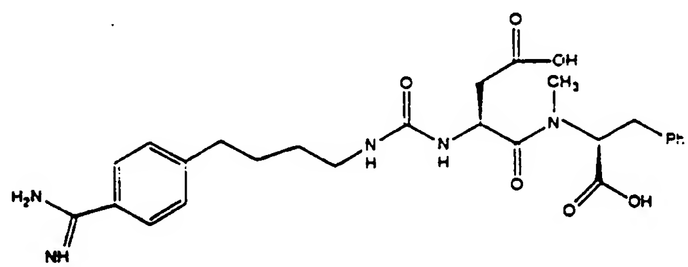


The title compound can be prepared substituting 3S-amino-4-[(2-carboxyethyl)(2-methylpropyl)amino]-4-oxobutanoic acid for aspartame in Section C of Example 1. The product is purified by reverse phase HPLC using the conditions of Example 1 to afford the title compound. The product is verified by C NMR and Chemical Ionization Mass Spectrometry.

Example 10

Preparation of

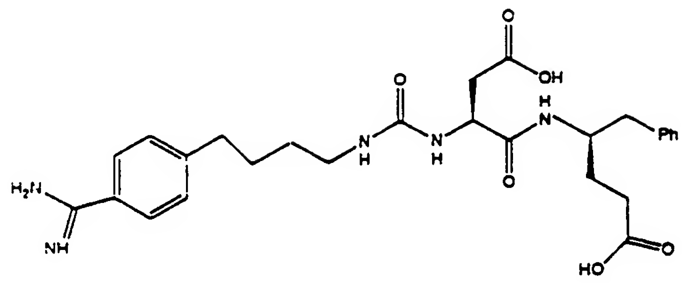
N-[N-[[[4-[4-(aminoiminomethyl)phenyl]-butyl]amino]-carbonyl]-L-α-aspartyl]-N-methyl-L-phenylalanine



The title compound can be prepared substituting L-α-aspartyl-N-methyl-L-phenylalanine for aspartame in Section C of Example 1. The product is purified by reverse phase HPLC using the conditions of Example 1 to afford the title compound. The product is verified by C NMR and Chemical Ionization Mass Spectrometry.

Example 11

Preparation of



The title compound can be prepared substituting R-3-[[carboxy-1-oxopropyl]amino]-5-phenylpentanoic acid for aspartame in Section C of Example 1. The product is purified by reverse phase HPLC using the conditions of Example 1 to afford the title compound. The product is verified by C NMR and Chemical Ionization Mass Spectrometry.

The platelet-binding inhibitor activity of the compounds of the present invention can be demonstrated by the assays presented below.

In-Vitro Platelet Aggregation in PRP

Healthy male or female dogs were fasted for 8 hours prior to drawing blood; then 30 ml whole blood was collected using a butterfly needle and 30 cc plastic syringe with 3 ml of 0.129 M buffered sodium citrate (3.8%). The syringe was rotated carefully as blood was drawn to mix the citrate. Platelet-rich plasma (PRP) was prepared by centrifugation at 975 x g for 3.17 minutes at room temperature, allowing the centrifuge to coast to a stop without braking. The PRP was removed from the blood with a plastic pipette and placed in a plastic capped, 50 ml Corning conical sterile centrifuge tube which was held at room temperature. Platelet poor plasma (PPP) was prepared by centrifuging the remaining blood at 2000 x g for 15 minutes at room temperature allowing the centrifuge to coast to a stop without braking. The PRP was adjusted with PPP to a count of 2-3 x 10^8 platelets per ml. 400 μl of the PRP preparation and 50 μl of the compound to be tested or saline were preincubated for 1 minute at 37°C in a BioData aggregometer (BioData, Horsham, PA). 50 μl of adenosine 5'-diphosphate (ADP) (50 μm final concentration) was added to the cuvettes and the aggregation was monitored for 1 minute. All compounds are tested in duplicate. Results are calculated as follows:

Percent of control = [(maximal OD minus initial OD of compound) divided by (maximal OD minus initial OD of control saline)] x 100. The % inhibition = 100 - (percent of control).

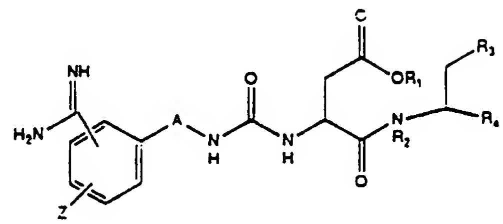
The assay results for the compounds of Examples 2 and 3 and their median inhibitory concentrations (IC_{50}) are recorded in Table I. IC_{50}'s (if a compound showed 50% inhibition) were calculated by linear regression of the dose response curve.

Table I

Example	Dog PRP IC_{50} Micro M
2	0.76
3	0.20

What is claimed is:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof wherein Z is selected from the group consisting of H, halogen, hydroxy, alkoxy of from one to six carbon atoms and alkyl of from one to six carbon atoms;

wherein A is selected from the group consisting of alkyl of one to six carbon atoms, alkenyl of two to six carbon atoms and alkynyl of two to six carbon atoms;

wherein R_1 is selected from the group consisting of H, alkyl of one to six carbon atoms, aralkyl and alkanoyloxyalkyl; and

wherein R_2 is selected from the group consisting of H, alkyl of one to six carbon atoms, and aralkyl optionally substituted with hydroxy and methoxy;

wherein R^3 is selected from the group consisting of alkyl, indolyl, pyridyl, benzothiophenyl, phenyl, benzofuranyl and furanyl all optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon

atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;

wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;

wherein m is an integer from 1 to 6; and

wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

2. A compound according to Claim 1 wherein
Z is hydrogen;
A is alkyl of one to six carbon atoms;
R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms;
R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy;
wherein R^3 is indolyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;
wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;
wherein m is an integer from 1 to 6; and

wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

3. A compound according to Claim 2 which is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-tryptophane.

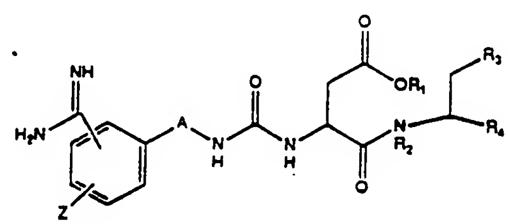
4. A compound according to Claim 1 wherein
Z is hydrogen;
A is alkyl of one to six carbon atoms;
R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms;
R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy;
wherein R^3 is phenyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;
wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;
wherein m is an integer from 1 to 6; and
wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

5. A compound according to Claim 4 which is N-[N-[[[4-[4-

(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester

6. A compound according to Claim 4 which is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine.

7. A pharmaceutical composition comprising a compound of the formula



or a pharmaceutically acceptable salt thereof wherein Z is selected from the group consisting of H, halogen, hydroxy, alkoxy of from one to six carbon atoms and alkyl of from one to six carbon atoms;

wherein A is selected from the group consisting of alkyl of one to six carbon atoms, alkenyl of two to six carbon atoms and alkynyl of two to six carbon atoms;

wherein R_1 is selected from the group consisting of H, alkyl of from one to six carbon atoms, aralkyl and alkanoyloxyalkyl; and

wherein R_2 is selected from the group consisting of H, alkyl of from one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy;

wherein R^3 is selected from the group consisting of alkyl, indolyl, pyridyl, benzothiophenyl,

benzofuranyl and furanyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;
wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;
wherein m is an integer from 1 to 6; and
wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to Claim 7 wherein
Z is hydrogen;
A is alkyl of one to six carbon atoms;
R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms; and
R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy;
wherein R^3 is indolyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;
wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;

wherein m is an integer from 1 to 6; and wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

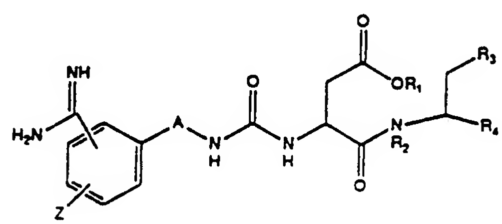
9. A pharmaceutical composition according to Claim 8 wherein the compound is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-L-α-aspartyl]tryptophane.

10. A pharmaceutical composition according to Claim 7 wherein Z is hydrogen;
A is alkyl of one to six carbon atoms;
R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms;
R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy;
wherein R^3 is phenyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;
wherein R^4 is selected from the consisting of H,-$COOR_5$ and -$(CH_2)_mCOOR_5$;
wherein m is an integer from 1 to 6; and wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

11. A pharmaceutical composition according to Claim 10 wherein the compound is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester

12. A pharmaceutical composition according to Claim 10 wherein the compound is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]amino]carbonyl]-L-α-aspartyl]-L-phenylalanine.

13. A method of treating a mammal to inhibit platelet aggregation comprising administering a therapeutically effective amount of a compound of the formula



or a pharmaceutically acceptable salt thereof wherein Z is selected from the group consisting of H, halogen, hydroxy, alkoxy of from one to six carbon atoms and alkyl of from one to six carbon atoms;
wherein A is selected from the group consisting of alkyl of one to six carbon atoms, alkenyl of two to six carbon atoms and alkynyl of two to six carbon atoms;

wherein R_1 is selected from the group consisting of H, alkyl of from one to six carbon atoms, aralkyl and alkanoyloxyalkyl; and
wherein R_2 is selected from the group consisting of H, alkyl of from one to six carbon atoms and aralkyl optionally substituted by hydroxy or methoxy;
wherein R^3 is selected from the group consisting of alkyl, indolyl, pyridyl, benzothiophenyl, benzofuranyl and furanyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;
wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;
wherein m is an integer from 1 to 6; and
wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

14. A method according to claim 13 wherein
Z is hydrogen;
A is alkyl of one to six carbon atoms;
R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms; and
R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy;
wherein R^3 is indolyl optionally substituted by a radical selected from the group consisting of

halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino; wherein R^4 is selected from the consisting of H,-$COOR_5$ and -$(CH_2)_mCOOR_5$; wherein m is an integer from 1 to 6; and wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

15. A method according to Claim 14 wherein the compound is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]-amino]carbonyl]-L-α-aspartyl]-L-tryptophane.

16. A method according to Claim 13 wherein Z is hydrogen; A is alkyl of one to six carbon atoms; R_1 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms; R_2 is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, and aralkyl optionally substituted by hydroxy or methoxy; wherein R^3 is phenyl optionally substituted by a radical selected from the group consisting of halogen, alkyl of one to six carbon atoms, alkoxy of one to six carbon atoms, carboxyl derivatives, nitro, cyano, azido, ureido, ureylene, alkoxycarbonyloxy, hydroxyl, alkylamino, alkoxycarbonyl, trialkylsilyl, alkoxyimino, alkylsulfonyl, phenylsulfonyl and amino;

wherein R^4 is selected from the consisting of H,-$COOR_5$ and $-(CH_2)_mCOOR_5$;
wherein m is an integer from 1 to 6; and
wherein R_5 is selected from the group consisting of H, alkyl of one to six carbon atoms and aralkyl.

17. A method according to Claim 16 wherein the compound is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]-amino]carbonyl]-L-α-aspartyl]-L-phenylalanine, diethyl ester

18. A method according to Claim 16 wherein the compound is N-[N-[[[4-[4-(aminoiminomethyl)phenyl]butyl]-amino]carbonyl]-L-α-aspartyl]-L-phenylalanine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/07975

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07K5/06 A61K37/02 C07C275/24 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP,A,0 513 675 (FUJISAWA PHARMCEUTICAL CO., LTD.) 19 November 1992 see compounds 14,26,31,55,72,74,83 see claims 1-5,7-10	1-18
P,X	WO,A,92 15607 (G.D. SEARLE & CO.) 17 September 1992 see claims; examples	1-18
A	EP,A,0 445 796 (F. HOFFMANN-LA ROCHE AG) 11 September 1991 cited in the application see claims	1,7,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search: 7 December 1993

Date of mailing of the international search report: 06 -01- 1994

Name and mailing address of the ISA
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Fax (+31-70) 340-3016

Authorized officer
Fuhr, C

International application No.
PCT/US93/07975

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claims 13-18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. …nal Application No

PCT/US 93/07975

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0513675	19-11-92	AU-A-	1614492	19-11-92
		CN-A-	1066660	02-12-92
		JP-A-	5148207	15-06-93
WO-A-9215607	17-09-92	AU-A-	1666692	06-10-92
		EP-A-	0502536	09-09-92
EP-A-0445796	11-09-91	JP-A-	4217652	07-08-92

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Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/096424 A1

(54) Title: HETEREOCYCLIC BETA-AMINOACIDS AND THEIR USE AS ANTI-EPILEPTOGENIC AGENTS

(57) Abstract: A method for preventing or treating epileptogenesis-associated diseases comprising the administration of a β-heterocyclic-β-aminoacid to a subject is disclosed. The disease can be for example head trauma, pain, stroke, anxiety, schizophrenia, psychosis, cerebral ischemia, Huntington's chorea, motor neuron disease, Alzheimer's disease, dementia of epilepsy.

HETEREOCYCLIC BETA-AMINOACIDS AND THEIR USE AS ANTI-EPILEPTOGENIC AGENTS

Related Applications

This application claims the priority of U.S. Provisional Patent Application No. 60/293,495, filed May 25, 2001, incorporated herein by reference.

Background of The Invention

Epilepsy is a serious neurological condition, associated with seizures, that affects hundreds of thousands of people worldwide. Clinically, a seizure results from a sudden electrical discharge from a collection of neurons in the brain. The resulting nerve cell activity is manifested by symptoms such as uncontrollable movements.

A seizure is a single discrete clinical event caused by an excessive electrical discharge from a collection of neurons through a process termed "ictogenesis." As such, a seizure is merely the symptom of epilepsy. Epilepsy is a dynamic and often progressive process characterized by an underlying sequence of pathological transformations whereby normal brain is altered, becoming susceptible to recurrent seizures through a process termed "epileptogenesis." While it is believed that ictogenesis and epileptogenesis have certain biochemical pathways in common, the two processes are not identical. Ictogenesis (the initiation and propagation of a seizure in time and space) is a rapid and definitive electrical/chemical event occurring over seconds or minutes. Epileptogenesis (the gradual process whereby normal brain is transformed into a state susceptible to spontaneous, episodic, time-limited, recurrent seizures, through the initiation and maturation of an "epileptogenic focus") is a slow biochemical and/or histological process which generally occurs over months to years. Epileptogenesis is a two phase process. Phase 1 epileptogenesis is the initiation of the epileptogenic process prior to the first seizure, and is often the result of stroke, disease (*e.g.*, meningitis), or trauma, such as an accidental blow to the head or a surgical procedure performed on the brain. Phase 2 epileptogenesis refers to the process during which a brain which is already susceptible to seizures, becomes still

more susceptible to seizures of increasing frequency and/or severity. While the processes involved in epileptogenesis have not been definitively identified, some researchers believe that upregulation of excitatory coupling between neurons, mediated by *N*-methyl-D-aspartate (NMDA) receptors, is involved. Other researchers implicate downregulation of inhibitory coupling between neurons, mediated by gamma-amino-butyric acid (GABA) receptors.

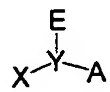
Although epileptic seizures are rarely fatal, large numbers of patients require medication to avoid the disruptive, and potentially dangerous, consequences of seizures. In many cases, medication is required for extended periods of time, and in some cases, a patient must continue to take prescription drugs for life. Furthermore, drugs used for the management of epilepsy have side effects associated with prolonged usage, and the cost of the drugs can be considerable.

A variety of drugs are available for the management of epileptic seizures, including older anticonvulsant agents such as phenytoin, valproate and carbamazepine (ion channel blockers), as well as newer agents such as felbamate, gabapentin, and tiagabine. β-Alanine has been reported to have anticonvulsant activity, as well as NMDA inhibitory activity and GABAergic stimulatory activity, but has not been employed clinically. Currently available accepted drugs for epilepsy are anticonvulsant agents, where the term "anticonvulsant" is synonymous with "anti-seizure" or "anti-ictogenic;" these drugs can suppress seizures by blocking ictogenesis, but it is believed that they do not influence epilepsy because they do not block epileptogenesis. Thus, despite the numerous drugs available for the treatment of epilepsy (i.e., through suppression of the convulsions associated with epileptic seizures), there are no generally accepted drugs for the treatment of the pathological changes which characterize epileptogenesis. There is no generally accepted method of inhibiting the epileptogenic process and there are no generally accepted drugs recognized as anti-epileptogenic.

Summary of The Invention

This invention relates to methods and compounds useful for the treatment of epileptogenesis-associated conditions such as, for example, epilepsy.

In one embodiment, the invention pertains to a method for inhibiting epileptogenesis in a subject. The method includes administering to the subject an effective amount of an anti-epileptogenic agent, such as, for example, β-heterocyclic-β-amino acid, or a compound of Formula I:



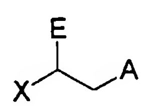
(I)

wherein X is a heterocyclic moiety, E is a hydrogen bond donor, Y is a connecting moiety, and A is an hydrogen bond acceptor, or a pharmaceutically acceptable salt, ester, *N*-substituted analog, or prodrug thereof.

In another embodiment, the invention pertains to a method for treating a subject suffering from an epileptogenesis-associated condition. The method includes administering to the subject an effective amount of an anti-epileptogenic agent, such as, for example, a β-heterocyclic-β-amino acid or a compound of Formula I.

The invention also pertains to a method for treating convulsions in a subject comprising administering to said subject an effective amount of an anti-epileptogenic agent (*e.g.*, a β-heterocyclic-β-amino acid or a compound of Formula I).

In yet another embodiment, the invention pertains, at least in part, to pharmaceutical compositions, comprising a therapeutically effective amount of an anti-epileptogenic agent and a pharmaceutical acceptable carrier, wherein said anti-epileptogenic agent is of the Formula (II):



(II) .

wherein X is a heterocyclic moiety, E is a hydrogen bond donor, Y is a connecting moiety, and A is an hydrogen bond acceptor, or a pharmaceutically acceptable salt, ester, *N*-substituted analog, or prodrug thereof.

In a further embodiment, the invention pertains, at least in part, to a method of diagnosing an epileptogenesis-associated condition in a subject. The method includes administering an anti-epileptogenic agent (*e.g.*, a compound of Formula I), labeled with a detectable marker to the subject; and measuring increased binding of the compound to the NMDA receptors of the neurons of the subject's brain.

In yet another embodiment, the invention pertains, at least in part, to a method of diagnosing an epileptogenesis-associated state. The method includes administering an anti-epileptogenic agent (*e.g.*, a compound of Formula 1) labeled with a detectable marker to a subject; and measuring decreased binding of the compound to the GABA receptors of the neurons of the subject's brain.

These and other objects, features, and advantages of the invention will be apparent from the following description and claims.

Detailed Description of The Invention

The present invention pertains to methods and agents useful for the treatment of epilepsy and convulsive disorders, for inhibition of epileptogenesis, and for inhibition of ictogenesis; and to methods for preparing the anti-epileptogenic agents of the invention. The invention further pertains to pharmaceutical compositions for treatment of epileptogenic conditions, and to kits including the anti-epileptogenic agents of the invention.

In one embodiment, the invention pertains to a method for inhibiting epileptogenesis in a subject. The method includes administering to the subject an effective amount of an anti-epileptogenic agent, such as, for example a β-heterocyclic-β-amino acid; *e.g.*, a β-heteroaromatic-β-amino acid.

The invention also pertains to methods for treating a subject suffering from an epileptogenesis-associated condition. The method includes administering to the subject an effective amount of an anti-epileptogenic agent (*e.g.*, a β-heterocyclic-β-amino acid, *e.g.*, a β-heteroaromatic-β-amino acid).

In another embodiment, the invention also includes a method for treating convulsions (*e.g.*, seizures) in a subject. The method includes administering to a subject

an effective amount of an anti-epileptogenic agent (e.g., a β-heterocyclic-β-amino acid, e.g., a β-heteroaromatic-β-amino acid).

The term "inhibiting epileptogenesis" includes both partial and complete reversal of epileptogenesis. It also includes prevention of epileptogenesis or a decrease or slowing in the rate of epileptogenesis (*e.g.*, a partial or complete stop in the rate of epileptogenic transformation of the brain or central nervous system tissue). It also includes any inhibition or slowing of the rate of the biochemical processes and/or events which take place during Phase 1 or Phase 2 epileptogenesis and leads to epileptogenic changes in tissue, *i.e.*, in tissues of the central nervous system (CNS), *e.g.*, the brain. Examples of processes in pathways associated with epileptogenesis, which may be inhibited by the compounds of the invention, are discussed in more detail, *infra*. It also includes the prevention, slowing, halting, or reversing the process of epileptogenesis, i.e., the changes in brain tissue which result in epileptic seizures.

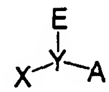
The term "convulsive disorder" or "convulsive condition" according to the invention includes conditions wherein a subject suffers from convulsions. Convulsive disorders include, but are not limited to, epilepsy, ictogenesis, epileptogenesis, and non-epileptic convulsions, and convulsions due to administration of a convulsive agent or trauma to the subject. The term "epileptogenesis-associated disorders" includes disorders of the central and peripheral nervous system which may advantageously be treated by the compounds of the invention. In an advantageous embodiment, the nervous system disorders are disorders associated or related to the process or the results of epileptogenic transformation of the brain or other nervous tissue. Examples of epileptogenesis-associated disorders include, but are not limited to, epilepsy, head trauma, pain, stroke, anxiety, schizophrenia, multiple sclerosis, amyloid lateral sclerosis, psychoses, cerebral ischemia, Huntington's chorea, motor neuron disease, Alzheimer's disease, dementia and other disorders (in humans or animals) in which excessive activity of NMDA receptors is a cause, at least in part, of the disorder (*see, e.g.*, Schoepp *et al.*, *Eur. J. Pharmacol. 203*:237-243 (1991); Leeson *et al.*, *J. Med. Chem. 34*:1243-1252 (1991); Kulagowski *et al.*, *J. Med. Chem. 37*:1402-1405 (1994); Mallamo *et al.*, *J. Med. Chem. 37*:4438-4448 (1994); and references cited therein).

The terms "treatment," "treating," or "treat," include the administration of an agent (*e.g.*, an anti-epileptogenic agent) to a subject, who has a disease or disorder, a symptom of a disease or disorder, or is at risk of suffering from the disease or disorder in the future, such that the disease or disorder (or at least one symptom of the disease or disorder) is cured, healed, prevented, alleviated, relieved, altered, remedied, ameliorated, improved or otherwise affected, preferably in an advantageous manner. Agents include, but are not limited to, anti-epileptogenic agents (*e.g.*, β-heterocyclic-β-amino acids).

The term "subject" includes animals susceptible to epileptogenesis or capable of suffering from epileptogenesis-associated states, such as warm-blooded animals, more preferably a mammal, including, *e.g.*, non-human animals such as rats, mice, cats, dogs, sheep, horses, cattle, in addition to humans. In a preferred embodiment, the subject is a human.

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent an epileptogenesis-associated state, *e.g.*, to prevent the various symptoms of an epileptogenesis-associated state. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular anti-epileptogenic agent. For example, the choice of the anti-epileptogenic agent can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the anti-epileptogenic agent without undue experimentation. The term "anti-epileptogenic agent" includes agents which are capable of, for example, inhibiting epileptogenesis, suppressing the uptake of synaptic GABA, blocking GABA transporters GAT-1, GAT-2 and/or GAT-3, depressing glutamatergic excitation, and/or interacting with an NMDA receptor (*e.g.*, at the strychnine insensitive glycine co-agonist site). Examples of anti-epileptogenic agents include β-heterocyclic-β-amino acids, *e.g.*, β-heteroaromatic-β-amino acids, and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

Other anti-epileptogenic agents of the invention include compounds of the Formula:



(I)

wherein:

X is a heterocyclic moiety;

Y is a connecting moiety;

E is a hydrogen bond donor; and

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

The term "heterocyclic moiety" ("X") includes both saturated and unsaturated heterocyclic rings. The heterocyclic moiety may be lipophilic and may be substituted with any substituent with allows the anti-epileptogenic agent to perform its intended function. Furthermore, the heterocyclic moiety may be stereochemically rigid and may contain, for example, one or more aromatic rings. The heterocyclic moiety also may comprise carbocyclic rings either bridged or fused to a heteroaromatic ring. In an embodiment, the heterocyclic moiety includes rings such as, for example, pyrrolidine, oxolane, thiolane, piperidine, piperazine, morpholine, lactones, lactams, azetidinones, pyrrolidinones, sultams, sultones, and the like.

Other examples of heterocyclic moieties include monocyclic heteroaryls such as, for example, thienyl, thiophenyl, pyrrolyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl, and furanyl.

In another embodiment, the heterocyclic moiety is multicyclic or polycyclic. The rings of the multicyclic or polycyclic heterocyclic moiety may be fused or bridged. In an embodiment, one of the bridged rings of the multicyclic heterocyclic moiety is phenyl (*e.g.*, when at least one other ring of the polycyclic heterocyclic moiety is heterocyclic (*e.g.*, thienyl, pyrrolyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isooxazolyl, thiazolyl,

isothiazolyl, imidazolyl, or furanyl). In an embodiment, the bridged heterocyclic moiety is isooxazolylphenyl (*e.g.*, an isooxazolyl ring bound to a phenyl ring).

In another further embodiment, the multicyclic (*e.g.*, bicyclic, tricyclic, etc.) heterocyclic moiety comprises one or more fused rings. In an embodiment, at least one of the fused rings is aromatic. In another, two or more of the rings in the fused ring system are aromatic. Examples of multicyclic fused ring heterocyclic moieties include, but are not limited to, benzothiazolonyl, indolonyl, benzooxoazolinyl, benzothiophenyl, benzofuranyl, quinolinyl, isoquinolinyl, benzodioxazolyl, benzoxazolyl, benzothiazolyl, benzoimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, indolyl, purinyl, and deazapurinyl.

Furthermore, each of the heterocyclic moieties described above, may be substituted with any substituent which allows the anti-epileptogenic agent to perform its intended function. Examples of substituents include, but are not limited to, alkyl (*e.g.*, methyl, ethyl, propyl, butyl, etc.), alkenyl, alkynyl, halogen (*e.g.*, fluorine, chlorine, bromine, iodine, etc.), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety.

According to the invention, the term "hydrogen bond donor" ("E") includes any moiety which is capable of being a hydrogen bond donor, such that the anti-epileptogenic agent is capable of performing its intended function. It also includes prodrugs of agents which are capable of being converted to the active form *in vivo*. Examples of hydrogen bond donors include, for example, NR^2R^3, CO_2H (including esters thereof, especially substituted or unsubstituted alkyl and aryl esters), OH, and SH, wherein R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl (*e.g.*, benzyl and 1- or 2-phenethyl, *i.e.*, α-methylbenzyl), alkylcarbonyl, arylcarbonyl (*e.g.*, benzoyl), alkoxycarbonyl, or aryloxycarbonyl (provided that at least one of R^2 and R^3 is

hydrogen). In one embodiment, the hydrogen bond donor is NH_2, OH, or SH. In an advantageous embodiment, the hydrogen bond donor is NH_2. A preferred hydrogen bond donor group is CO_2H.

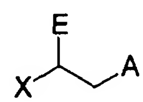
According to the invention, the term "hydrogen bond acceptor" ("A") includes any moiety which is capable of forming an electrostatic bond with a hydrogen atom of a hydrogen bond donor, such that the anti-epileptogenic agent is capable of performing its intended function. It also includes prodrugs of agents which are capable of being converted to the active form *in vivo*. In a preferred embodiment, hydrogen bond acceptors include anionic moieties, including moieties having a free electron pair, such as an amine (NR^2R^3, wherein R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl (*e.g.*, benzyl and 1- or 2-phenethyl, *i.e.*, α-methylbenzyl), alkylcarbonyl, arylcarbonyl (*e.g.*, benzoyl), alkoxycarbonyl, or aryloxycarbonyl), OH, and SH. A preferred hydrogen bond acceptor is NH_2.

The term "anionic moiety" includes moieties which are either anionic under physiological conditions, polar, or chosen such that they allow the anti-epileptogenic agent to perform its intended function. Pharmaceutically acceptable salts of anionic moieties as well as their protonated forms are also included. Furthermore, prodrugs are also included, wherein a moiety may be converted to its active, or more active form once administered to a subject. Examples of prodrugs include esters which can be converted to carboxylate groups *in vivo*. Examples of anionic moieties include, but are not limited to, carboxylate (*e.g.*, carboxylic acids), sulfate, sulfonate, sulfinate, nitrates, nitrites, sulfamate, phosphate, phosphonate, tetrazolyl, phosphinate, phosphorothioate, or functional equivalents thereof. Advantageous anionic moieties include carboxylate, carboxylic acids, and prodrugs thereof. "Functional equivalents" of anionic groups are intended to include bioisosteres, *e.g.*, bioisosteres of a carboxylate group. Bioisosteres encompass both classical bioisosteric equivalents and non-classical bioisosteric equivalents. Classical and non-classical bioisosteres are known in the art (*see*, *e.g.*, Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, Inc.: San Diego, CA, 1992, pp.19-23).

The term "connecting moiety" ("Y") includes moieties which connect (*e.g.*, through covalent bonds) each of the hydrogen bond acceptor, the hydrogen bond donor,

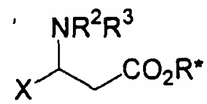
and the heterocyclic moieties. In an embodiment, the connecting moiety comprises 1 to 20 atoms; and in a preferred embodiment, the connecting moiety comprises or consists of 1 to 6 carbon atoms (with the appropriate number of hydrogens). In another embodiment, the connecting moiety is selected such that the anti-epileptogenic agent of the invention is capable of performing its intended function, *e.g.*, inhibiting epileptogenesis, treating nervous system disorders, agonizing the NMDA receptor, suppressing uptake of synaptic GABA, etc. In another embodiment, the connecting moiety is selected such that the anti-epileptogenic compound of the invention is capable of being transported through the blood brain barrier. In one embodiment, the connecting moiety is comprised of from one to five carbon atoms, optionally substituted with hydrogen or another substituent which allows the agent to perform its intended function. In a further embodiment, the connecting moiety is alkyl, *e.g.*, selected such that the resulting anti-epileptogenic agent is a β-amino acid.

In one embodiment, the anti-epileptogenic agent of the invention is of the Formula (II):



(II)

In a further preferred embodiment, the anti-epileptogenic agent of the invention is a β-amino-β-heterocyclic-1-propionic acid of the Formula (IIa):



(IIa)

wherein:

R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl (*e.g.*, benzyl and 1- or 2-phenethyl, *i.e.*, α-methylbenzyl), alkylcarbonyl, arylcarbonyl (*e.g.*, benzoyl), alkoxycarbonyl, or aryloxycarbonyl;

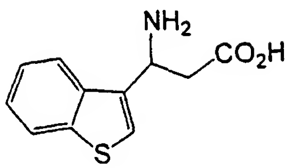
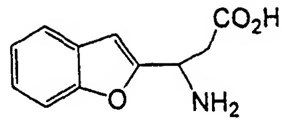
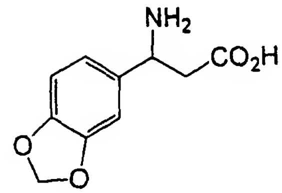
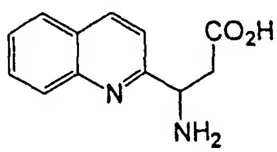
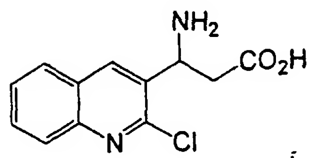
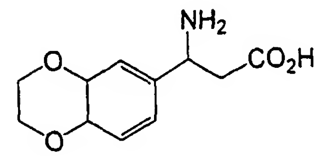
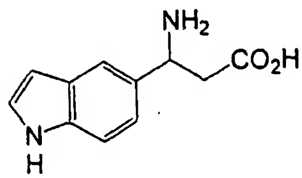
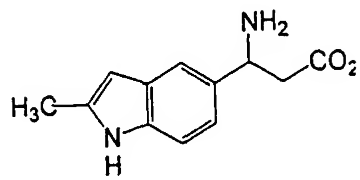
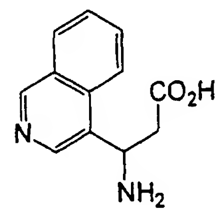
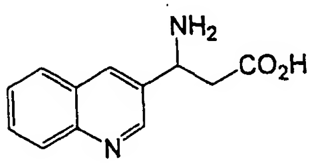
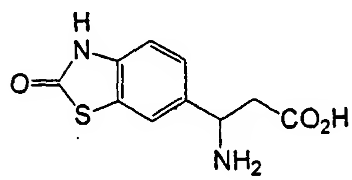
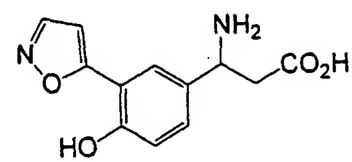
X is a heterocyclic moiety; and

R* is a substituted or unsubstituted alkyl moiety, a substituted or unsubstituted aryl moiety, a hydrogen, or a physiologically acceptable cation.

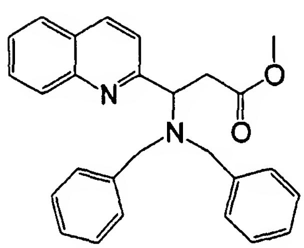
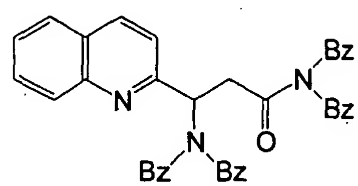
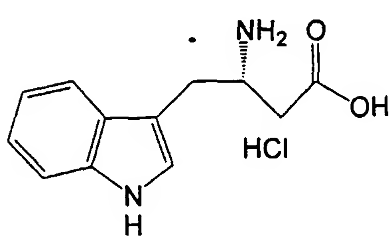
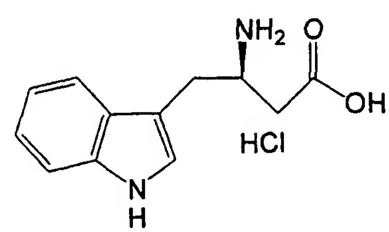
Examples of prodrugs include moieties which can be converted *in vivo* to the agents of the invention (*see*, *e.g.*, R.B. Silverman, 1992, cited above, Chp. 8). Such prodrugs can be used to alter the biodistribution (*e.g.*, to allow compounds which would not typically cross the blood-brain barrier to cross the blood-brain barrier) or the pharmacokinetics of the therapeutic compound. For example, anionic moieties (*e.g.*, a carboxylate, sulfonate, etc.) can be esterified, *e.g.*, with a methyl group or a phenyl group, to yield a carboxylate or sulfonate ester. When the carboxylate or sulfonate ester is administered to a subject, the ester is cleaved, enzymatically or non-enzymatically, to yield the anionic moiety. Such an ester can be cyclic, *e.g.*, a lactone or sultone, or two or more anionic moieties may be esterified through a linking group. An anionic moiety can be esterified with groups (*e.g.*, acyloxymethyl esters) which are cleaved to reveal an intermediate compound which subsequently decomposes to yield the active compound. Alternatively, an anionic moiety can be esterified to a group which is actively transported *in vivo*, or which is selectively taken up by target organs. The ester can be selected to allow specific targeting of the therapeutic moieties to particular organs. In another embodiment, the prodrug is a reduced form of an anionic group, *e.g.*, a carboxylate or sulfonate, *e.g.*, an alcohol or thiol, which is oxidized *in vivo* to the therapeutic compound.

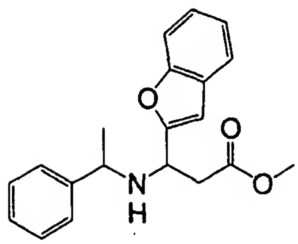
Examples of anti-epileptogenic agents of Formula II, include but are not limited to, 3-(benzo[b]thiophen-3-yl)-3-aminopropionic acid, 3-(benzo[b]furan-2-yl)-3-aminopropionic acid, 3-(benzo[b]dioxolan-5-yl)-3-aminopropionic acid, 3-(quinolin-2-yl)-3-aminopropionic acid, 3-(2-chloroquinolin-3-yl)-3-aminopropionic acid, 3-(benzo[b]dioxan-6-yl)-3-aminopropionic acid, 3-(indol-4-yl)-3-aminopropionic acid, 3-(7-methylindol-4-yl)-aminopropionic acid, 3-(isoquinolin-4-yl)-3-aminopropionic acid, 3-(quinolin-3-yl)-3-aminopropionic acid, 3-(benzo[b]thiazolinon-5-yl)-3-aminopropionic acid, 3-(4-hydroxy-3-isoxazol-5-ylphenyl)-3-aminopropionic acid, and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

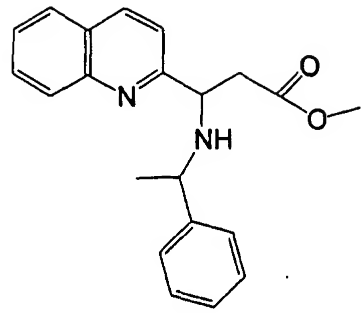
Examples of anti-epileptogenic agents also include:

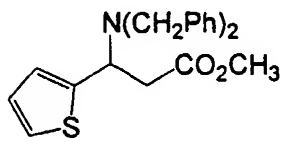
Further preferred examples of anti-epileptogenic agents include:

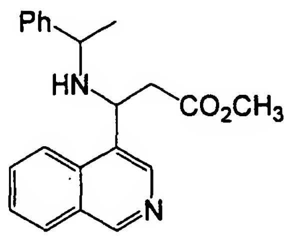









Still further examples of anti-epileptogenic agents include:





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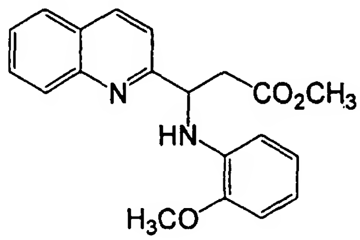
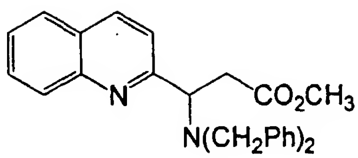
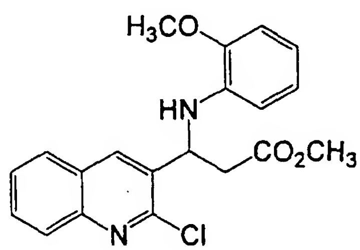






The heteroaryl groups represented in the example compounds above are therefore within the invention, *i.e.*, those heteroaryl groups may be "X" in any Formula herein.

The β-heteroaryl-β-amino acid compounds of the invention can be synthesized using art recognized techniques and/or the procedures described herein. For example, β-heteroaryl-acrylic acid esters are accessible by reacting the corresponding heteroaryl aldehydes or heteroarylbromides via the Horner-Wadsworth-Emmons reaction or the Heck reaction, respectively (for reviews of the HWE reaction, *see* Wadsworth, *Org. React.* (1997) 25:73-253; *Acc. Chem. Res.* (1983) 16:411-417; Wadsworth *J. Am. Chem. Soc.* (1961) 83:1733; for reviews of the Heck reaction, see Heck, *Palladium Reagents in Organic Syntheses;* Academic Press: New York, 1985, pp. 179-321). The β-heteroaryl acrylic acid esters can also be treated (via a Michael addition) with secondary lithium amides to yield protected β-heteroaryl-β-amino acids (see, for example, March, *Advanced Organic Chemistry;* John Wiley & Sons: New York, 1992, pp. 795-797, and references cited therein). The protected β-amino acids can be deprotected and saponified to yield the β-heteroaryl-β-amino acids of the invention. The synthetic methods of the invention are described in greater detail in Example 1.

In one embodiment, the compounds described herein do not include those mentioned in published PCT application WO 98/40055, incorporated herein by reference in its entirety.

The term "alkenyl" includes unsaturated aliphatic groups containing a carbon-carbon double bond, including straight-chain alkenyl groups, branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups, alkenyl substituted cycloalkyl or cycloalkenyl groups, and cycloalkenyl substituted alkyl or alkenyl groups. The term alkenyl further includes alkenyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In an embodiment, a straight chain or branched chain alkenyl group has 20 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_{20} for straight chain, C_3-C_{20} for branched chain).

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted

cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In preferred embodiments, a straight chain or branched chain alkyl has 10 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_{10} for straight chain, C_3-C_{10} for branched chain), and more preferably 6 or fewer. Likewise, preferred cycloalkyls have from 4-7 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing one or more hydrogens on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "alkylaryl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (*i.e.*, benzyl)).

The term "aryl" includes aryl groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, benzoxazole, benzothiazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl groups also include polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy,

aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.*, tetralin).

The terms "alkenyl" and "alkynyl" include unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively. Examples of substituents of alkynyl groups include, for example alkyl, alkenyl (*e.g.*, cycloalkenyl, *e.g.*, cyclohexenyl), and aryl groups.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to three carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

The terms "alkoxyalkyl," "polyaminoalkyl," and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, *e.g.*, oxygen, nitrogen or sulfur atoms.

The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (*e.g.*, cycloalkyls, cycloalkenyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, *e.g.*, the rings are "fused rings." Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term “alkylsulfinyl” include groups which have one or more sulfinyl (SO) linkages, typically 1 to about 5 or 6 sulfinyl linkages. Advantageous alkylsulfinyl groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms.

The term “alkylsulfonyl” includes groups which have one or more sulfonyl (SO_2) linkages, typically 1 to about 5 or 6 sulfonyl linkages. Advantageous alkylsulfonyl groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms.

The term “alkanoyl” includes groups having 1 to about 4 or 5 carbonyl groups. The term “aroyl” includes aryl groups, such as phenyl and other carbocyclic aryls, which have carbonyl substituents. The term “alkaroyl” includes aryl groups with alkylcarbonyl substituents, *e.g.*, phenylacetyl.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in

substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, alkenes can include either the *E*- or *Z*- geometry, where appropriate.

The invention also pertains, at least in part, to novel compounds *per se*, *e.g.*, anti-epileptogenic agents, described herein. Furthermore, the invention also pertains to pharmaceutical compositions comprising each of the chemical compounds described herein and packaged pharmaceutical compositions comprising any chemical compound described herein, packaged with directions relating to using the compounds to treat a nervous system disorder, *e.g.*, an epileptogenic disorder, *e.g.*, epilepsy.

In one embodiment, the invention provides a method for inhibiting epileptogenesis in a subject. The method includes the step of administering to a subject in need thereof an effective amount of a compound (*e.g.*, an anti-epileptogenic agent of the invention, *e.g.*, a β-heterocyclic-β-amino acid) which modulates a process in a pathway associated with epileptogenesis, such that epileptogenesis is inhibited in the subject.

As noted above, upregulation of excitatory coupling between neurons, mediated by *N*-methyl-D-aspartate (NMDA) receptors, and downregulation of inhibitory coupling between neurons, mediated by gamma-amino-butyric acid (GABA) receptors, have both been implicated in epileptogenesis. Other processes in pathways associated with epileptogenesis include release of nitric oxide (NO), a neurotransmitter implicated in epileptogenesis; release of calcium (Ca^{2+}), which may mediate damage to neurons when released in excess; neurotoxicity due to excess zinc (Zn^{2+}); neurotoxicity due to excess iron (Fe^{2+}); and neurotoxicity due to oxidative cell damage. Accordingly, in preferred embodiments, an agent to be administered to a subject to inhibit epileptogenesis preferably is capable of inhibiting one or more processes in at least one pathway associated with epileptogenesis. For example, an agent useful for inhibition of epileptogenesis can reduce the release of, or attenuate the epileptogenic effect of, NO in brain tissue; antagonize an NMDA receptor; augment endogenous GABA inhibition; block voltage-gated ion channels; reduce the release of, reduce the free concentration of (*e.g.*, by chelation), or otherwise reduce the epileptogenic effect of cations including Ca^{2+}, Zn^{2+}, or Fe^{2+}; inhibit oxidative cell damage; or the like. In certain preferred embodiments, an agent to be

administered to a subject to inhibit epileptogenesis is capable of inhibiting at least two processes in at least one pathway associated with epileptogenesis.

In one preferred embodiment, the anti-epileptogenic agent antagonizes an NMDA receptor and augments endogenous GABA inhibition. In certain embodiments, the anti-epileptogenic agent is administered orally; preferably, after the step of oral administration, the anti-epileptogenic agent is transported to the nervous system of the subject by an active transport shuttle mechanism. A non-limiting example of an active transport shuttle is the large neutral amino acid transporter, which is capable of transporting amino acids across the blood-brain barrier (BBB).

The step of administering to a subject an anti-epileptogenic compound of the invention, *e.g.*, a β-heterocyclic-β-amino acid or a compound of any Formula herein, can include administration to the subject of an anti-epileptogenic agent of the invention, an anti-epileptogenic agent in its active form, optionally in a pharmaceutically acceptable carrier. The step of administering to the subject can also include administering to the subject an agent which is metabolized to an anti-epileptogenic compound of the invention. For example, the methods of the invention include the use of prodrugs which are converted *in vivo* to the agents of the invention (*see, e.g.*, R.B. Silverman, 1992, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, Chp. 8). Such prodrugs can be used to alter the biodistribution (*e.g.*, to allow compounds which would not typically cross the blood-brain barrier to cross the blood-brain barrier) or the pharmacokinetics of the agent. For example, the anionic moiety, *e.g.*, a carboxylate group, can be esterified, *e.g.*, with an ethyl group or a fatty group, to yield a carboxylic ester. When the carboxylic ester is administered to a subject, the ester can be cleaved, enzymatically or non-enzymatically, to reveal the anionic moiety.

In an embodiment, an anti-epileptogenic agent of the invention may antagonize NMDA receptors by interacting, *e.g.*, binding to the glycine binding site of the NMDA receptors. In another embodiment, the agent augments GABA inhibition by decreasing glial GABA uptake. In certain other embodiments, the method further includes administering the agent in a pharmaceutically acceptable vehicle, *e.g.*, such that the anti-epileptogenic agent is suitable, *e.g.*, for oral administration.

In still another embodiment, the invention provides a method of treating (*e.g.*, preventing, alleviating, modulating, etc.) convulsions (*e.g.*, seizures, *e.g.*, associated with epilepsy, trauma, etc.). The method includes the step of administering to a subject (*e.g.*, a subject suffering from, or at risk of suffering from convulsions or a disorder characterized by convulsions or seizures) an effective amount of an anti-epileptogenic compound of the invention such that the convulsive disorder is treated. Examples of anti-epileptogenic agents of the invention include compounds such as β-heterocyclic-β-amino acids and compounds of any Formula herein.

In another embodiment, the invention provides a method for inhibiting both a convulsive condition and epileptogenesis in a subject. The method includes the step of administering to a subject in need thereof an effective amount of an agent which a) blocks sodium or calcium ion channels, or opens potassium or chloride ion channels; and b) has at least one activity selected from the group consisting of NMDA receptor antagonism; augmentation of endogenous GABA inhibition; calcium binding; iron binding; zinc binding; NO synthase inhibition; and antioxidant activity; such that epileptogenesis is inhibited in the subject.

Blockers of sodium and/or calcium ion channel activity are well known in the art and can be used as the A moiety in the compounds and methods of the present invention. Similarly, any compound which opens potassium or chloride ion channels can be used as the A moiety in the compounds and methods of the present invention. Antagonists of NMDA receptors and augmenters of endogenous GABA inhibition are also known to one of skill in the art and can be used in the methods and compounds of the invention. For example, 2,3-quinoxalinediones are reported to have NMDA receptor antagonistic activity (*see*, *e.g.*, U.S. Patent No. 5,721,234). Exemplary calcium and zinc chelators include moieties known in the art for chelation of divalent cations, including (in addition to those mentioned *supra*) ethylenediaminetetraacetic acid (EDTA), ethylene glycol bis(beta-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid, and the like. Exemplary iron chelators include enterobactin, pyridoxal isonicotinyl hydrazones, *N,N'*-bis(2-hydroxybenzoyl)-ethylenediamine-*N,N'*-diacetic acid (HBED), 1-substituted-2-alkyl-3-hydroxy-4-pyridones, including 1-(2'-carboxyethyl)-2-methyl-3-hydroxy-4-pyridone, and other moieties known in the art to chelate iron. Compounds which inhibit NO synthase activity are known in the

art and include, *e.g.*, Nγ -substituted arginine analogs (especially of the L configuration), including L-Nγ-nitro-arginine (a specific inhibitor of cerebral NO synthase), L-Nγ-amino-arginine, and L-Nγ-alkyl-arginines; or an ester (preferably the methyl ester) thereof. Exemplary antioxidants include ascorbic acid, tocopherols including alpha-tocopherol, and the like.

Anti-epileptogenic agents of the invention can be identified through screening assays. For example, the animal model of Phase 1 epileptogenesis described in Examples 2-5, *infra*, can be employed to determine whether a particular compound has anti-epileptogenic activity against Phase 1 epileptogenesis. Chronic epileptogenesis can be modeled in rats (and candidate compounds screened with) the kindling assay described by Silver *et al.* (*Ann. Neurol.* (1991) 29:356). Similarly, compounds useful as anti-convulsants can be screened in conventional animal models, such as the mouse model described in Hotrod, R.W. *et al.*, *Eur. J. Pharmacol.* (1979) 59:75-83. Compounds or pharmacophores useful for, *e.g.*, binding to or inhibition of receptors or enzymes can be screened according to conventional methods known to the ordinarily skilled artisan. For example, binding to the GABA uptake receptor can be quantified by the method of Ramsey *et al.* as modified by Schlewer (Schlewer, J., *et al.*, *J. Med. Chem.* (1991) 34:2547). Binding to the glycine site on an NMDA receptor can be quantified, *e.g.*, according to the method described in Kemp, A., *et al.*, *Proc. Natl. Acad. Sci. USA* (1988) 85:6547. Effect on the voltage-gated Na^+ channel can be evaluated *in vitro* by voltage clamp assay in rat hippocampal slices.

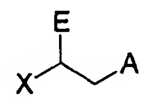
Assays suitable for screening candidate compounds for anticonvulsive and/or anti-epileptogenic activity in mice or rats are described in Examples 2-5, *infra*.

In a further embodiment, the invention pertains, at least in part, to a method of diagnosing an epileptogenesis-associated condition in a subject. The method includes administering an anti-epileptogenic agent (*e.g.*, a compound of any Formula herein), labeled with a detectable marker to the subject; and measuring increased binding of the compound to the NMDA receptors of the neurons of the subject's brain.

In yet another embodiment, the invention pertains, at least in part, to a method of diagnosing an epileptogenesis-associated state. The method includes administering an

anti-epileptogenic agent (*e.g.*, a compound of any Formula herein) labeled with a detectable marker to a subject; and measuring decreased binding of the compound to the GABA receptors of the neurons of the subject's brain.

In one embodiment, the invention pertains to pharmaceutical compositions, which include an effective amount of an anti-epileptogenic agent and a pharmaceutical acceptable carrier. The anti-epileptogenic agent may be a β-heterocyclic-β-amino acid (*e.g.*, a β-heteroaromatic-β-amino acid), or a compound of Formula II:



(II)

wherein:

X is a heterocyclic moiety;

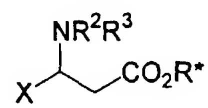
E is a hydrogen bond donor;

Y is a connecting moiety;

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

In another embodiment, the anti-epileptogenic agent in a pharmaceutical composition of the invention is of the Formula (IIa):



(IIa)

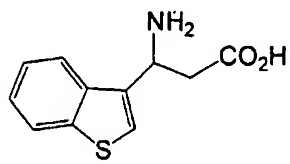
wherein:

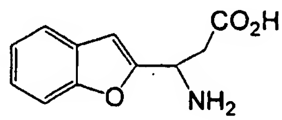
R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl (*e.g.*, benzyl and 1- or 2-phenethyl, *i.e.*, α-methylbenzyl), alkylcarbonyl, arylcarbonyl (*e.g.*, benzoyl), alkoxycarbonyl, or aryloxycarbonyl;

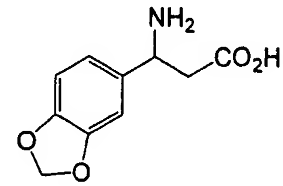
X is a heterocyclic moiety; and

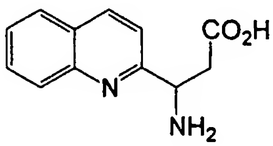
R* is a substituted or unsubstituted alkyl moiety, a substituted or unsubstituted aryl moiety, a hydrogen, or a physiologically acceptable cation.

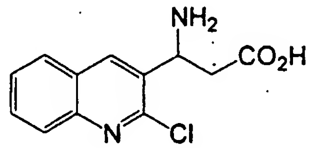
Other anti-epileptogenic agents which may be formulated into therapeutic compositions of the invention, include, but are not limited to, agents such as:

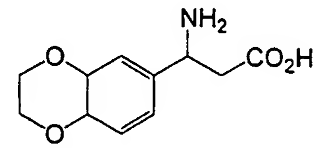


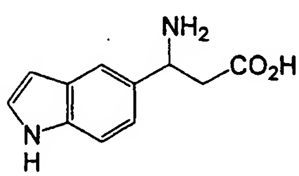


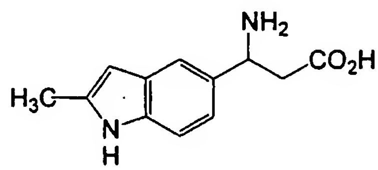


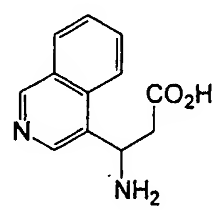


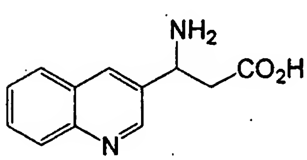


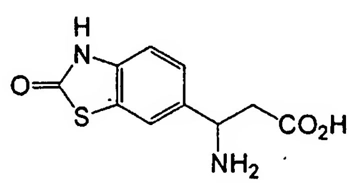


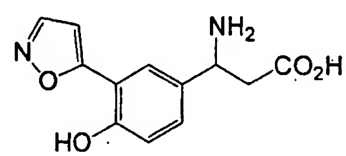


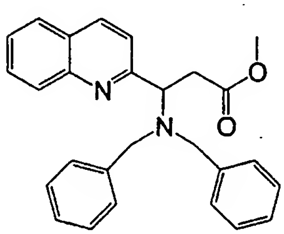


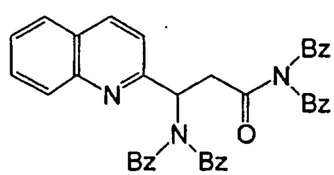


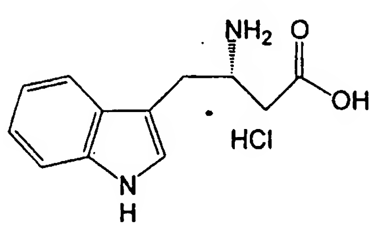


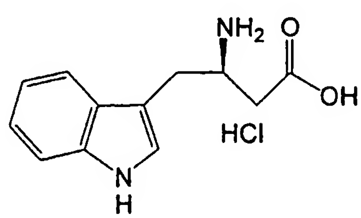


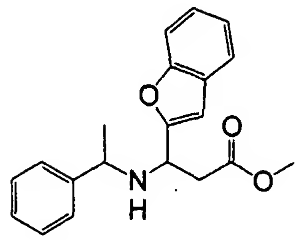


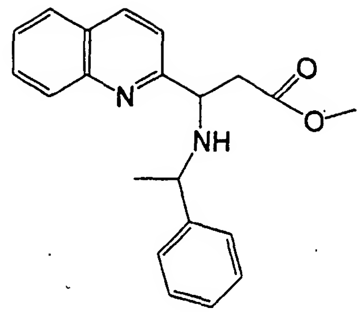


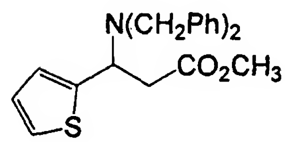


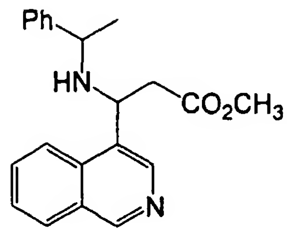


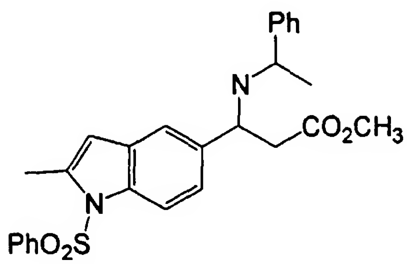


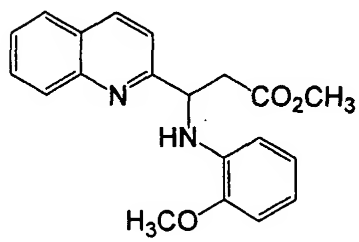


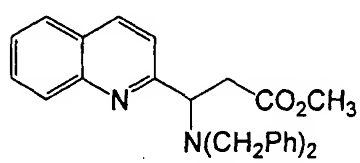


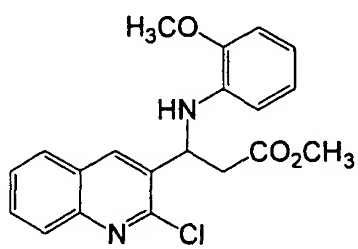












and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

In a further embodiment, the effective amount is effective to treat an epileptogenesis-associated state in a subject. Examples of such states, include, but are not limited to, epilepsy, head trauma, pain, stroke, anxiety, schizophrenia, other psychoses, cerebral ischemia, Huntington's chorea, motor neuron disease, Alzheimer's disease, and dementia.

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the agents described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally or intrarectally, for example, as a pessary, cream or foam. In a preferred embodiment, the therapeutic compound is administered orally. The agents of the invention can be formulated as pharmaceutical compositions for administration to a subject, *e.g.*, a mammal, including a human.

The agents of the invention are administered to subjects in a biologically compatible form suitable for pharmaceutical administration *in vivo*. By "biologically compatible form suitable for administration *in vivo*" is meant an agent to be administered in which any toxic effects are outweighed by the therapeutic effects of the agent. The term "subject" is intended to include living organisms in which an immune response can be elicited, *e.g.*, mammals. Examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof. Administration of a therapeutically active amount of the therapeutic compositions of the present invention is defined as an amount effective, at dosages and for periods of time necessary to achieve the desired result. For example, a therapeutically active amount of an agent of the invention may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of agent to elicit a desired response in the individual. Dosage regimes may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The active agent may be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application,

or rectal administration. Depending on the route of administration, the active agent may be coated in a material to protect the agent from the action of enzymes, acids and other natural conditions which may inactivate the agent.

An agent of the invention can be administered to a subject in an appropriate carrier or diluent, co-administered with enzyme inhibitors or in an appropriate carrier such as liposomes. The term "pharmaceutically acceptable carrier" as used herein is intended to include diluents such as saline and aqueous buffer solutions. To administer an agent of the invention by other than parenteral administration, it may be necessary to coat the agent with, or co-administer the agent with a material to prevent its inactivation. Liposomes include water-in-oil-in-water emulsions as well as conventional liposomes (Strejan *et al.*, (1984) *J. Neuroimmunol* 7:27). The active agent may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The pharmaceutically acceptable carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the

composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating active agent in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active agent into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

When the active agent is suitably protected, as described above, the composition may be orally administered, for example, with an inert diluent or an edible carrier. As used herein "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active agent, use thereof in the therapeutic compositions is contemplated. Supplementary active agents can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. "Dosage unit form," as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active agent and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active agent for the therapeutic treatment of individuals.

EXEMPLIFICATION OF THE INVENTION

All assays are performed by the Anticonvulsant Drug Development (ADD) Program in the Epilepsy Branch of the NIH (*see, e.g.*, Stables and Kupferberg (1997) *The NIH anticonvulsant Drug Development (ADD) Program: Preclinical Anticonvulsant Screening Project*, Libby & Sons). All compounds are tested with either male Carworth Farms #1 mice or male Sprague-Dawley rats. Each test compound is administered *via* an i.p. injection at 300, 100, and 30 mg/kg.

Example 1 Synthesis of Some Compounds of the Invention

One skilled in the art will appreciate that the synthetic chemistry protocols described herein may be modified with no more than routine experimentation to arrive at analogous compounds which are therefore also within the scope of the present invention.

3-Amino-3-(quinolin-2-yl)-1-propionic Acid

In a solution of acetonitrile, 2-quinolinecarboxaldehyde is treated with 3-(dimethoxy-phosphoryl)-acetic acid methyl ester (Bhattcharya et al., *Chem. Rev.* (1981) 81:415) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and lithium chloride (Wadsworth, *Org. Reac.* 1977 25:73-253), to yield the β-quinolin-2-yl-acrylic acid ester. The acrylic acid ester is then treated with (1-Phenyl-ethyl)-trimethylsilanyl-amine in THF at –78 °C to yield the product via a Michael addition (J. G. Rico et al., *J. Org. Chem.* 58:27 7948-7951 (1993)).

3-Amino-3-(Benzo[d]-1,3-dioxolan-5-yl)propionic Acid

A mixture of benzo[d]-1,3-dioxolane-5-carboxaldehyde (3.04 g; 20.2 mmol), malonic acid (2.10 g; 20.1 mmol) and ammonium acetate (3.09 g; 40.1 mmol) in dry EtOH (40 mL) was refluxed for 6.5 hr. The resulting white solid was collected *via* filtration and triturated with EtOH (50 mL). A white powder was collected *via* filtration (0.78 g; 18%): mp 223-224 °C; R_f 0.24 (A); R_f 0.33 (B); ν_{max} (KBr): 3448, 2890, 1632, 1571, 1446, 1037 cm^{-1}; m/z (ES): 210.1, 117.0. 76.0, 59.0; δ_H (D_2O, K_2CO_3, 400 MHz): 2.38 (1 H, dd, J = 14.5 and 7.1), 2.45 (1 H, dd, J = 14.5 and 7.7), 4.07 (1 H, t, J = 7.4), 5.81 (2 H, d, J = 1.2), 6.74 (2 H, d, J = 0.8), 6.80 (1 H, s); δ_C (D_2O, K_2CO_3, 101 MHz): 46.9, 53.0, 101.3,

107.1, 108.7, 120.1, 138.7, 146.3, 147.4, 180.2; m/z calculated for $C_{10}H_{11}NO_4$: 210.0766 (MH^+), found 210.0766 (MH^+).

3-Amino-3-(Benzo[e]-1,4-dioxan-6-yl)propionic Acid

A mixture of benzo[e]-1,4-dioxane-6-carboxaldehyde (3.29 g; 20.0 mmol), malonic acid (2.08 g; 20.0 mmol) and ammonium acetate (3.10 g; 40.2 mmol) in dry EtOH (40 mL) was refluxed for 6.5 hr. The resulting white solid was collected *via* filtration and triturated with EtOH (50 mL). A white powder was collected *via* filtration (0.94 g; 13%): mp 222-223 °C; R_f 0.23 (A); R_f 0.37 (B); ν_{max} (KBr): 3443, 2875, 1631, 1564, 1071 cm^{-1}; m/z (ES): 224.1, 178.0, 117.0, 59.0; δ_H (D_2O, K_2CO_3, 400 MHz): 2.37 (1 H, dd, J = 15.4 and 6.9), 2.42 (1 H, dd, J = 14.5 and 7.8), 4.03 (1 H, t, J = 7.4), 4.13 (4 H, s), 6.75 (2 H, s), 6.77 (1 H, s); δ_C (D_2O, K_2CO_3, 101 MHz): 46.9, 52.6, 64.8, 115.3, 117.5, 119.9, 138.2, 142.2, 143.0, 180.3; m/z calculated for $C_{11}H_{13}NO_4$: 224.0923 (MH^+), found 224.0923 (MH^+).

3-(Quinolin-2-yl)acrylic Acid Methyl Ester

To a stirred suspension of lithium chloride (1.02 g; 24.1 mmol) in dry MeCN (200 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals trimethyl phosphonoacetate (4.39 g; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g; 20.0 mmol) in dry MeCN (10 mL) and finally quinoline-2-carboxaldehyde (3.15 g; 20 mmol) in dry MeCN (30 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting amber oil was dissolved in DCM (75 mL) and washed with distilled water (5 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by column chromatography on silica gel using EtOAc:DCM (1:19) as the eluent followed by recrystallization with EtOAc and hexanes gave a yellow crystalline solid (2.75g; 65%): mp 85-86 °C; R_f 0.62 (D); R_f 0.20 (E); ν_{max} (KBr): 1733, 1282, 1121, 981 cm^{-1}; m/z (EI): 213.0, 182.0, 153.9; δ_H ($CDCl_3$, 200 MHz): 3.85 (3 H, s), 7.00 (1 H, d, J = 15.8), 7.56 (1 H, ddd, J = 8.0, 6.8 and 1.2), 7.61 (1 H, d, J = 8.2), 7.74 (1 H, ddd, J = 8.2, 6.8 and 1.4), 7.83 (1 H, dd, J = 8.4 and 1.0), 7.90 (1 H, d, J = 15.8), 8.10 (1 H, dq, J = 8.4 and 1.0), 8.18 (1 H, d, J = 8.6); δ_C ($CDCl_3$, 126 MHz): 51.9, 120.2, 120.9, 123.1, 125.7, 126.4,

127.1, 127.2, 128.9, 129.9, 135.3, 136.6, 144.1, 147.2, 158.1, 173.1; m/z calculated for $C_{13}H_{11}NO_2$: 213.0790 (M^+), found 213.0796 (M^+).

3-(Quinolin-2-yl)acrylic Acid t-Butyl Ester

To a stirred suspension of lithium chloride (0.82 g; 19.3 mmol) in dry MeCN (140 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals *t*-butyl *P,P*-dimethyl phosphonoacetate (4.31 g; 19.2 mmol) in dry MeCN (10 mL), DBU (2.43 g; 16.0 mmol) in dry MeCN (10 mL) and finally quinoline-2-carboxaldehyde (2.52 g; 16.0 mmol) in dry MeCN (30 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting amber oil was dissolved in DCM (50 mL) and washed with distilled water (4 x 25 mL) and saturated sodium chloride solution (4 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by recrystallization with EtOAc and hexanes gave a yellow crystalline solid (2.54 g; 62%): mp 96-97 °C; R_f 0.53 (C); R_f 0.38 (E); ν_{max} (KBr): 3048, 1704, 1298, 1144, 992 cm^{-1}; m/z (EI): 255.1, 182.0, 153.8; δ_H ($CDCl_3$, 200 MHz): 1.56 (9 H, s), 6.90 (1 H, d, J = 16.0), 7.56 (1 H, dd, J = 7.0 and 1.2), 7.62 (1 H, d, J = 8.6), 7.74 (1 H, ddd, J = 8.6, 6.8 and 1.6), 7.80 (1 H, dd, J = 8.2 and 1.0), 7.81 (1 H, d, J = 15.6), 8.12 (1 H, d, J = 8.6), 8.18 (1 H, d, J = 9.0); δ_C ($CDCl_3$, 126 MHz): 28.0, 80.6, 119.8, 125.6, 126.9, 127.3, 127.7, 129.5, 129.7, 136.4, 142.8, 148.0, 153.3, 165.5; m/z calculated for $C_{16}H_{17}NO_2$: 255.1260 (M^+), found 255.1268 (M^+).

3-(2-Chloroquinolin-3-yl)acrylic Acid Methyl Ester

To a stirred suspension of lithium chloride (1.02 g; 24.1 mmol) in dry MeCN (185 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals trimethyl phosphonoacetate (4.39 g; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g, 20.0 mmol) in dry MeCN (10 mL) and finally 2-chloroquinoline-3-carboxaldehyde (3.87 g; 20.1 mmol) in dry MeCN (40 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting amber oil was dissolved in DCM (75 mL) and washed with distilled water (6 x 25 mL). The organic layer was dried over

sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by recrystallization with EtOAc and hexanes gave a yellow crystalline solid (2.52 g; 51%): mp 153-154 °C; R_f 0.65 (D); R_f 0.46 (E); ν_{max} (KBr): 1711, 1262, 1184, 980 cm^{-1}; m/z (EI): 247.0, 212.1, 153.1, 139.9, 127.1, 75.4; δ_H ($CDCl_3$, 200 MHz): 3.86 (3 H, s), 6.57 (1 H, dd, J = 16.0 and 0.4), 7.60 (1 H, ddd, J = 8.2, 7.0 and 1.2), 7.78 (1 H, ddd, J = 8.4, 7.0 and 1.4), 7.86 (1H, dd, J = 7.2 and 1.0), 8.02 (1 H, dd, J = 8.2 and 0.6), 8.14 (1 H, dd, J = 16.0 and 0.8), 8.84 (1 H, s); δ_H ($CDCl_3$, 126 MHz): 53.4, 123.7, 129.1, 129.4, 129.8, 131.9, 133.0, 137.2, 137.5, 141.1, 149.3, 151.4, 167.8; m/z calculated for $C_{13}H_{10}NO_2Cl$: 247.0400 (M^+), found 247.0406 (M^+).

3-(Benzo[d]thiophen-3-yl)acrylic Acid Methyl Ester

To a stirred suspension of lithium chloride (1.02g; 24.1 mmol) in dry MeCN (180 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals trimethyl phophonoacetate (4.39 g; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g; 20.0 mmol) in dry MeCN and finally benzo[d]thiophen-3-carboxaldehyde (3.24 g; 20.0 mmol) in dry MeCN (30 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting yellow oil was dissolved in DCM (60 mL) and washed with distilled water (3 x 20 mL) and saturated sodium chloride solution (3 x 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a red oil. Purification by column chromatography on silica gel using DCM as the eluent followed by recrystallization with hexanes gave a pale yellow crystalline solid (2.63 g; 60%): mp 63-65 °C; R_f 0.68 (D); R_f 0.45 (F); ν_{max} (KBr): 1708, 1281, 1159, 972 cm^{-1}; m/z (EI): 218.0, 187.0, 159.1, 88.8; δ_H ($CDCl_3$, 200 MHz): 3.84 (3 H, s), 6.54 (1 H, d, J = 15.8), 7.41 (1 H, td, J = 5.6 and 1.8), 7.47 (1 H, td, J = 5.6 and 1.6), 7.76 (1 H, s), 7.88 (1 H, dq, J = 7.0 and 2.2), 7.98 (1 H, dd, J = 16.4 and 0.6), 8.02 (1 H, dq, J = 5.0 and 1.4); δ_C ($CDCl_3$, 101 MHz): 52.1, 118.6, 122.4, 123.3, 124.6, 125.4, 128.4, 131.9, 136.9, 137.4, 140.8, 167.9; m/z calculated for $C_{12}H_{10}O_2S$: 218.0402 (M^+), found 218.0401 (M^+).

3-(Benzo[d]furan-2-yl)acrylic Acid Methyl Ester

To a stirred suspension of lithium chloride (1.02g; 24.1 mmol) in dry MeCN (200 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals trimethyl phosphonoacetate (4.39; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g; 20.0 mmol) in dry MeCN (10 mL) and finally benzo[b]furan-2-carboxaldehyde (2.92 g; 20.0 mmol) in dry MeCN (15 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting yellow oil was dissolved in DCM (50 mL) and washed with distilled water (3 x 20 mL) and saturated sodium chloride solution (3 x 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give an off-white solid. Purification by recrystallization with hexanes gave an off-white crystalline solid (3.98; 98%): mp 84-86 °C; R_f 0.60 (E); R_f 0.51 (C); ν_{max} (KBr): 3116, 1699, 1657, 1268, 1185, 956, 758 cm^{-1}; m/z (EI): 202.0, 171.0, 143.0, 130.9, 88.8; δ_H ($CDCl_3$, 200 MHz): 3.82 (3 H, s), 6.58 (1 H, d, J = 15.8), 6.94 (1 H, s), 7.23 (1 H, td, J = 7.2 and 1.2), 7.36 (1 H, td, J = 7.2 and 1.6), 7.48 (1 H, dq, J = 8.8 and 0.8), 7.56 (1 H, d, J = 16.0), 7.58 (1 H, dq, J = 7.8 and 0.8); δ_C ($CDCl_3$, 126 MHz): 51.6, 111.0, 111.2, 118.3, 121.6, 123.1, 126.3, 128.2, 131.3, 152.1, 155.4, 166.9; m/z calculated for $C_{12}H_{10}O_3$: 202.0630 (M^+), found 202.0638 (M^+).

3-(Benzo[d]furan-2-yl)acrylic Acid t-Butyl Ester

To a stirred suspension of lithium chloride (1.02g; 24.1 mmol) in dry MeCN (175 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals *t*-butyl *P,P*-dimethyl phosphonoacetate (5.38; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g; 20.0 mmol) in dry MeCN (10 mL) and finally benzo[b]furan-2-carboxaldehyde (2.92 g; 20.0 mmol) in dry MeCN (40 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting yellow oil was dissolved in DCM (60 mL) and washed with distilled water (3 x 25 mL) and saturated sodium chloride solution (3 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography with

EtOAc:hexanes (1:4) as the eluent gave a white powder (4.28 g; 89%): mp 56-57 °C; R_f 0.58 (C); R_f 0.82 (L); ν_{max} (KBr): 1694, 1635, 1295, 1161, 985 cm^{-1}; m/z (EI): 244.1, 188.0, 170.8, 131.0, 117.9, 114.8; δ_H ($CDCl_3$, 400 MHz): 1.56 (9 H, s), 6.54 (1 H, d, J = 15.7), 6.90 (1 H, s), 7.24 (1 H, td, J = 7.9 and 1.0), 7.35 (1 H, td, J = 7.2 and 1.3), 7.46 (1 H, d, J = 15.7), 7.47 (1 H, dd, J = 8.3 and 0.8), 7.58 (1 H, dd, J = 7.3 and 0.7); δ_C ($CDCl_3$, 101 MHz): 28.5, 81.0, 110.7, 111.7, 121.4, 122.0, 123.5, 126.5, 128.7, 130.6, 152.9, 155.8, 166.2; m/z calculated for $C_{15}H_{16}O_3$: 244.1099 (M^+), found 244.1104 (M^+).

3-(Benzo[e]-1,4-dioxan-6-yl)acrylic Acid Methyl Ester

To a stirred suspension of lithium chloride (1.02 g; 24.1 mmol) in dry MeCN (170 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals trimethyl phophonoacetate (4.39 g; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g, 20.0 mmol) in dry MeCN (15 mL) and finally benzo[e]-1,4-dioxane-6-carboxaldehyde (3.29 g; 20.0 mmol) in dry MeCN (40 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting yellow oil was dissolved in DCM (50 mL) and washed with distilled water (4 x 20 mL) and saturated sodium chloride solution (3 x 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by recrystallization with EtOAc and hexanes gave a pale yellow crystalline solid (3.97 g; 90%): mp 66-68 °C; R_f 0.52 (E); R_f 0.30 (C); ν_{max} (KBr): 3013, 1708, 1693, 1281, 1172, 1152, 980, 804 cm^{-1}; m/z (EI): 220.0, 204.9, 189.0, 161.0, 150.9, 58.9; δ_H ($CDCl_3$, 200 MHz): 3.78 (3 H, s), 4.27 (4 H, s), 6.27 (1 H, d, J = 16.0), 6.85 (1 H, dt, J = 8.2 and 0.6), 7.00 (1 H, ddd, J = 8.8, 2.2, and 0.4), 7.04 (1 H, d, J = 0.6), 7.57 (1 H, d, J = 15.6); δ_H ($CDCl_3$, 126 MHz): 51.2, 64.0, 64.3, 115.6, 116.4, 117.4, 121.8, 127.8, 143.5, 144.2, 145.5, 167.3; m/z calculated for $C_{12}H_{12}O_4$: 220.0736 (M^+), found: 220.0740 (M^+).

3-(Benzo[d]dioxolan-5-yl)acrylic Acid t-Butyl Ester

To a stirred suspension of lithium chloride (1.02 g; 24.0 mmol) in dry MeCN (175 mL) under nitrogen at room temperature was added drop-wise at 15 min intervals *t*-butyl *P,P*-dimethyl phosphonoacetate (5.38 g; 24.0 mmol) in dry MeCN (15 mL), DBU (3.05 g; 20.0 mmol) in dry MeCN (10 mL) and finally benzo[d]dioxolane-5-

carboxaldehyde (3.01 g; 20.0 mmol) in dry MeCN (40 mL). The reaction was allowed to stir at room temperature until completion, as determined by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The resulting yellow oil was dissolved in DCM (60 mL) and washed with distilled water (3 x 25 mL) and saturated sodium chloride solution (3 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give an off-white solid. Purification by recrystallization with MeOH gave a white crystalline solid (2.70 g; 54%): mp 82-83 °C; R_f 0.69 (D); R_f 0.63 (E); ν_{max} (KBr): 1699, 1635, 1248, 1145, 1100, 971 cm^{-1}; m/z (EI):248.2, 191.0, 175.0, 147.1, 145.0, 116.9, 89.0, 65.0; δ_H ($CDCl_3$, 400 MHz): 1.53 (9 H, s), 5.99 (2 H, s), 6.20 (1 H, d, J = 15.9), 6.79 (1 H, d, J = 8.0), 6.97 (1 H, dd, J = 8.0 and 1.5), 7.02 (1 H, d, J = 1.4), 7.49 (1 H, d, J = 15.9); δ_C ($CDCl_3$, 101 MHz): 28.5, 80.6, 101.8, 106.8, 108.9, 118.5, 124.4, 129.4, 143.5, 148.6, 149.6, 166.8; m/z calculated for $C_{14}H_{16}O_4$: 248.1049 (M^+), found 248.1055 (M^+).

3-(Indol-5-yl)acrylic Acid Methyl Ester

A mixture of 5-bromoindole (1.97 g, 10.0 mmol), methyl acrylate (1.08 g, 12.5 mmol), palladium acetate (24.9 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (0.61 g, 2.0 mmol) and triethylamine (3.62 g, 35.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 100 °C for 2 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (3 x 25 mL), dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by recrystallization with EtOAc and hexanes gave a yellow powder (1.53 g; 76%): mp 138-140 °C; R_f 0.29 (C); R_f 0.51 (E); ν_{max} (KBr): 3316, 1694, 1284, 988 cm^{-1}; m/z (EI): 201.0, 170.0, 142.1, 116.1, 84.9; δ_H ($CDCl_3$, 200 MHz): 3.81 (3 H, s), 6.42 (1 H, d, J = 15.4), 6.59 (1 H, t, J = 2.4), 7.24 (1 H, d, J = 3.0), 7.42 (2 H, t, J = 1.2), 7.81 (1 H, s), 7.84 (1 H, d, J = 15.8), 8.34 (1 H, bs); δ_C ($CDCl_3$, 126 MHz): 51.4, 103.1, 111.6, 114.2, 121.3, 122.3, 125.5, 126.1, 128.0, 137.1, 146.9, 168.3; m/z calculated for $C_{12}H_{11}NO_2$: 201.0790 (M^+), found 201.0790 (M^+).

3-(2-Methylindol-5-yl)acrylic Acid Methyl Ester

A mixture of 5-bromo-2-methylindole (2.10 g, 10.0 mmol), methyl acrylate (1.08 g, 12.5 mmol), palladium acetate (23.2 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (61.3 g,

0.2 mmol) and triethylamine (3.62 g, 35.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 100 °C for 3 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (3 x 25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow solid. Purification by recrystallization with EtOAc gave a pale yellow powder (1.57 g; 73%): mp 172-173 °C; R_f 0.35 (C); R_f 0.61 (E); ν_{max} (KBr): 3295, 1698, 1305, 1282, 1165, 975 cm^{-1}; m/z (EI): 215.1, 184.1, 156.1, 77.2; δ_H ($CDCl_3$, 400 MHz): 2.45 (3 H, s), 3.82 (3 H, s), 6.25 (1 H, s), 6.42 (1 H, d, J = 16.0), 7.27 (1 H, d, J = 8.0), 7.35 (1 H, d, J = 8.0), 7.69 (1 H, s), 7.85 (1 H, d, J = 16.0), 8.15 (1 H, bs); δ_C ($CDCl_3$, 101 MHz): 14.0, 51.8, 101.5, 111.0, 114.5, 121.1, 121.4, 126.5, 129.7, 136.7, 137.7, 147.4, 168.6; m/z calculated for $C_{13}H_{13}NO_2$: 215.0946 (M^+), found 215.0945 (M^+).

N-(t-Butyldimethyl)-3-(2-Methylindol-5-yl)acrylic Acid t-Butyl Ester

A mixture of *N*-(*t*-butyldimethyl)-5-bromo-2-methylindole (1.30 g, 4.0 mmol), *t*-butyl acrylate (0.64 g, 5.0 mmol), palladium acetate (25.6 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (63.5 g, 0.2 mmol) and triethylamine (1.45 g, 14.3 mmol) was heated under argon in a heavy-walled Pyrex tube at 100 °C for 3 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (3 x 25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow oil. Purification by column chromatography using EtOAc:hexanes (1:9) as the eluent followed by recrystallization with hexanes gave a white powder (0.94 g; 63%): mp 102-103 °C; R_f 0.40 (H); R_f 0.33 (M); ν_{max} (KBr): 2951, 1708, 1631, 1302, 1271, 1150, 990 cm^{-1}; m/z (EI): 371.4,315.3, 298.3, 258.2, 184.0, 155.9, 129.1, 115.0; δ_H ($CDCl_3$, 400 MHz): 0.65 (6 H, s), 0.98 (9 H, s), 1.56 (9 H, s), 2.49 (3 H, d, J = 0.5), 6.34 (1 H, d, J = 15.9), 6.35 (1 H, s), 7.27 (1 H, dd, J = 6.5 and 1.8), 7.47 (1 H, d, J = 8.7), 7.63 (1 H, d, J = 1.6), 7.71 (1 H, d, J = 15.9); δ_C ($CDCl_3$, 101 MHz): -0.2, 17.8, 20.9, 27.0, 28.6, 80.2, 106.9, 114.7, 117.2, 120.4, 120.5, 126.8, 132.0, 143.6, 144.3, 145.6, 167.4; m/z calculated for $C_{22}H_{33}NO_2Si$: 371.2281 (M^+), found 371.2297 (M^+).

<u>*3-(Quinolin-3-yl)acrylic Acid Methyl Ester*</u>

A mixture of 3-bromoquinoline (2.08 g, 10.0 mmol), methyl acrylate (1.08 g, 12.5 mmol), palladium acetate (23.6 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (0.122 g, 0.4 mmol) and triethylamine (3.62 g, 35.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 100 °C for 6 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (3 x 25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow solid. Purification by recrystallization with EtOAc and hexanes gave an off-white crystalline solid (1.82 g; 85%): mp 124-125 °C; R_f 0.19 (C); R_f 0.10 (E); ν_{max} (KBr): 1716, 1635, 1263, 1174, 983 cm^{-1}; m/z (EI): 213.0, 182.3, 154.2, 128.5; δ_H ($CDCl_3$, 200 MHz): 3.84 (3H, s), 6.67 (1 H, d, J = 16.2), 7.60 (1 H, ddd, J = 8.2, 7.2 and 1.4), 7.77 (1 H, ddd, J = 8.4, 7.0 and 1.6), 7.84 (1 H, d, J = 16.2), 7.86 (1 H, dd, J = 7.0 and 1.4), 8.14 (1 H, d, J = 8.6), 8.26 (1 H, d, J = 2.2), 9.09 (1 H, d, J = 2.2); δ_C ($CDCl_3$, 126 MHz): 51.7, 119.6, 127.2, 127.3, 127.4, 128.1, 129.2, 130.4, 135.3, 141.2, 148.4, 149.0, 166.7; m/z calculated for $C_{13}H_{11}O_2N$: 213.0790 (M^+), found 213.0790 (M^+).

<u>*3-(Quinolin-3-yl)acrylic Acid t-Butyl Ester*</u>

Procedure 1: A mixture of 3-bromoquinoline (2.08 g, 10.0 mmol), *t*-butyl acrylate (1.60 g, 12.5 mmol), palladium acetate (25.1 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (0.130 g, 0.4 mmol) and triethylamine (3.62 g, 35.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 100 °C for 6 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (3 x 25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by recrystallization with EtOAc and hexanes gave a pale yellow crystalline solid (2.43 g; 95%): mp 128-129 °C; R_f 0.32 (D); R_f 0.24 (L); ν_{max} (KBr): 1694, 1635, 1295, 1161, 984 cm^{-1}; m/z (EI): 255.0, 198.8, 181.8, 169.9, 154.1, 126.5; δ_H ($CDCl_3$, 200 MHz): 1.55 (9 H, s), 6.58 (1 H, d, J = 16.4), 7.56 (1 H, td, J = 8.0 and 1.2), 7.72 (1 H, d, J = 16.4), 7.73 (1 H, td, J = 8.2 and 1.4), 7.82 (1 H, dd, J = 8.2 and 1.2), 8.20

(1 H, d, J = 2.2), 9.05 (1 H, d, J = 2.2); δ_C ($CDCl_3$, 101 MHz): 28.5, 81.3, 122.5, 127.7, 127.9, 128.0, 128.6, 29.6, 130.8, 135.7, 140.4, 148.6, 149.5, 166.0; m/z calculated for $C_{16}H_{17}O_2N$: 255.1259 (M^+), found 255.1251 (M^+).

Procedure 2: A mixture of 3-bromoquinoline (1.56 g, 7.5 mmol), *t*-butyl acrylate (13.1 g, 102 mmol), palladium acetate (0.106 g, 0.4 mmol) and triethylamine (1.09 g, 10.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 80 °C for 36 h. Palladium acetate (0.100 g; 0.4 mmol) was again added and the mixture stirred for a further 36 h. The cooled reaction mixture was filtered and concentrated under reduced pressure to give an amber oil. Purification by column chromatography using EtOAc:DCM (1:9) as the eluent gave a pale yellow crystalline solid (0.228 g; 12%).

3-(Isoquinolin-4-yl)acrylic Acid Methyl Ester

A mixture of 4-bromoisoquinoline (2.08 g, 10.0 mmol), methyl acrylate (1.08 g, 12.5 mmol), palladium acetate (24.2 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (1.22 g, 4.0 mmol) and triethylamine (3.62 g, 35.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 100 °C for 46 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (4 x 25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by recrystallization with EtOAc and hexanes gave a yellow powder (1.41 g; 66%): mp 79-80 °C; R_f 0.10 (C); R_f 0.07 (E); ν_{max} (KBr): 1716, 1631, 1318, 1176, 976 cm^{-1}; m/z (EI): 213.0, 181.9, 154.0, 128.1; δ_H ($CDCl_3$, 200 MHz): 3.87 (3H, s), 6.61 (1 H, d, J = 15.8), 7.71 (1 H, ddd, J = 8.4, 6.8 and 1.2), 7.85 (1 H, ddd, J = 8.0, 6.8 and 1.2), 8.07 (1 H, d, J = 8.2), 8.17 (1 H, d, J = 7.6), 8.36 (1 H, d, J = 15.8), 8.74 (1 H, s), 9.29 (1 H, s); δ_C ($CDCl_3$, 126 MHz): 51.7, 121.7, 122.4, 125.4, 127.5, 127.9, 128.1, 131.0, 133.4, 138.7, 141.4, 153.8, 166.6; m/z calculated for $C_{13}H_{11}NO_2$: 213.0790 (M^+), found 213.0786 (M^+).

3-(Isoquinolin-4-yl)acrylic Acid t-Butyl Ester

Procedure 1: A mixture of 4-bromoisoquinoline (2.08 g, 10.0 mmol), *t*-butyl acrylate (1.60 g, 12.5 mmol), palladium acetate (25.7 mg, 0.1 mmol), tri(*o*-tolyl)phosphine (0.132 g, 0.4 mmol) and triethylamine (3.62 g, 35.8 mmol) was heated under argon in a

heavy-walled Pyrex tube at 100 °C for 46 h. The cooled reaction mixture was diluted with DCM (60 mL) and distilled water (30 mL). The organic layer was washed with distilled water (4 x 25 mL). The aqueous layer was extracted with DCM (25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography with EtOAc:DCM (1:9) as the eluent followed by recrystallization with hexanes gave a pale yellow crystalline solid (1.95 g; 76%).

Procedure 2: A mixture of 4-bromoisoquinoline (1.25 g, 6.0 mmol), *t*-butyl acrylate (13.1 g, 102 mmol), palladium acetate (0.102 g, 0.4 mmol) and triethylamine (1.09 g, 10.8 mmol) was heated under argon in a heavy-walled Pyrex tube at 80 °C for 36 h. Palladium acetate (0.102 g; 0.4 mmol) was again added and the mixture stirred for a further 36 h. The cooled reaction mixture was filtered and concentrated under reduced pressure to give an amber oil. Purification by column chromatography using EtOAc:DCM (1:9) as the eluent gave a tan solid (80.6 mg; 5%): mp 81-83 °C; R_f 0.19 (C); R_f 0.22 (L); ν_{max} (KBr): 1702, 1627, 1318, 1150, 970 cm^{-1}; m/z (EI): 255.2, 199.1, 182.0, 154.0, 126.9, 76.8; δ_H ($CDCl_3$, 400 MHz): 1.57 (9 H, s), 6.51 (1 H, d, J = 15.9), 7.64 (1 H, t, J = 7.3), 7.77 (1 H, td, J = 7.0 and 1.1), 7.99 (1 H, d, J = 8.2), 8.12 (1 H, d, J = 8.5), 8.24 (1 H, d, J = 15.9), 8.72 (1 H, s), 9.21 (1H, s); δ_C ($CDCl_3$, 101 MHz): 28.5, 81.3, 123.0, 124.7, 126.3, 127.9, 128.4, 131.5, 134.0, 137.8, 141.6, 153.9, 166.0; m/z calculated for $C_{13}H_{11}NO_2$: 255.1259 (M^+), found 255.1266 (M^+).

3-(Thiophen-2-yl)acrylic Acid Methyl Ester

To a stirred solution of 3-(thiophen-2-yl)acrylic acid (3.08 g: 20.0 mmol) in dry MeOH (75 mL) at 0 °C under nitrogen was added drop-wise thionyl chloride (4.89 g; 40.0 mmol). The resulting mixture was allowed to warm to room temperature and refluxed until completion, as determined by TLC. To the reaction mixture was added activated carbon. The resulting mixture was filtered and concentrated under reduced pressure to give a tan solid (2.54 g; 76%): mp 52-54 °C; R_f 0.88 (A); R_f 0.53 (C); ν_{max} (KBr): 1708, 1306, 1164, 986, 703 cm^{-1}; m/z (EI): 168.0, 137.0, 108.7, 83.1; δ_H ($CDCl_3$, 200 MHz): 3.75 (3 H, s), 6.21 (1 H, d, J = 15.8), 7.01 (1 H, t, J = 4.4), 7.21 (1 H, d, J = 3.2), 7.33 (1 H, d, J = 5.0), 7.76 (1 H, d, J = 15.4); δ_C ($CDCl_3$, 126 MHz): 51.4, 116.4, 127.9, 128.2,

130.7, 137.0, 139.3, 167.0; m/z calculated for $C_8H_8O_2S$: 168.0245 (M^+), found 168.0246 (M^+).

N,N-(Dibenzyl)-3-Amino-3-(Thiophen-2-yl)propionic Acid Methyl Ester

To a stirred solution of dibenzylamine (0.789 g; 4.00 mmol) in dry THF (30 mL) at 0 °C under nitrogen was added drop-wise n-butyl lithium (1.6 M in hexanes; 2.5 mL; 4.0 mmol). The resulting red solution was stirred at 0 °C for 15 min and cooled to -78 °C. 3-(thiophen-2-yl)acrylic acid methyl ester (0.340 g, 2.02 mmol) in dry THF (8 mL) was added drop-wise at –78 °C and stirred for 15 min before quenching with saturated ammonium chloride solution (4 mL). The reaction mixture was allowed to warm to room temperature and poured into saturated sodium chloride solution (50 mL). The aqueous layer was separated and extracted with diethyl ether (2 x 40 mL). The combined organic layers were washed with saturated sodium chloride solution (2 x 10 mL), dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow oil. Purification by column chromatography on silica gel with Et_2O:hexanes (1:4) as the eluent gave white crystals (0.378 g; 51%): mp 88-90 °C; R_f 0.56 (C); R_f 0.29 (G); ν_{max} (KBr): 1739, 1609, 1294, 1257, 1116, 1021, 697 cm^{-1}; m/z (CI): 366.2, 292.1, 198.0, 168.9, 90.9, 82.8; δ_H ($CDCl_3$, 200 MHz): 2.78 (1 H, dd, J = 14.8 and 7.0), 3.07 (1 H, dd, J = 13.1 and 8.0), 3.36 (2 H, d, J = 13.6), 3.64 (3 H, s), 3.71 (2 H, d, J = 13.8), 4.54 (1 H, t, J = 7.2), 6.90 (1 H, dq, J = 3.4 and 1.2), 7.01 (1 H, ddd, J = 5.0, 3.4 and 0.8), 7.18-7.41 (11 H, m); δ_C ($CDCl_3$, 126 MHz): 37.6, 51.5, 53.7, 54.8, 124.5, 125.4, 126.4, 127.0, 128.1, 128.9, 139.2, 142.0, 171.5; m/z calculated for $C_{22}H_{23}NO_2S$: 365.1450 (M^+), found 365.1451 (M^+).

N,N-(Dibenzyl)-3-Amino-3-(Quinolin-2-yl)propionic Acid Methyl Ester and N,N,N',N'-(Tetrabenzyl)-3-Amino-3-(Quinolin-2-yl)-Propionoamide

To a stirred solution of dibenzylamine (3.95 g; 20.0 mmol) in dry THF (150 mL) at 0 °C under nitrogen was added drop-wise *n*-butyl lithium (1.6 M in hexanes; 12.5 mL; 20.0 mmol). The resulting red solution was stirred at 0 °C for 15 min and cooled to -78 °C. 3-(Quinolin-2-yl)acrylic acid methyl ester (2.13 g; 10.0 mmol) in dry THF (30 mL) was added drop-wise at –78 °C and stirred for 15 min before quenching with saturated ammonium chloride solution (20 mL). The reaction mixture was allowed to warm to room

temperature and poured into saturated sodium chloride solution (50 mL). The aqueous layer was separated and extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with saturated sodium chloride solution (3 x 40 mL), dried over sodium sulfate and concentrated under reduced pressure to give an amber oil. Purification by column chromatography on silica gel with Et_2O: hexanes (1:2) as the eluent followed by purification by recrystallization with Et_2O and hexanes gave two products. A yellow crystalline solid (Ester: 0.64 g; 16%): mp 101-102 °C; R_f 0.56 (E); R_f 0.30 (C); ν_{max} (KBr): 3058, 1728, 1296, 1218 cm^{-1}; m/z (CI): 411.3, 215.0, 155.9, 91.0; δ_H ($CDCl_3$, 200 MHz): 3.08 (1 H, dd, J = 16.0 and 4.0), 3.42 (1 H, dd, J = 15.4 and 9.2), 3.64 (4 H, s), 3.66 (3 H, s), 4.63 (1 H, dd, J = 8.4 and 4.4), 7.20-7.40 (10 H, m), 7.50 (1 H, t, J = 7.0), 7.57 (1 H, d, J = 8.6), 7.67 (1 H, td, J = 7.0 and 1.6), 7.79 (1 H, d, J = 8.2), 8.03 (1 H, d, J = 8.4), 8.12 (1 H, d, J = 8.4); δ_C ($CDCl_3$, 126 MHz): 31.0, 51.5, 59.8, 121.9, 126.1, 127.0, 127.3, 127.4, 128.3, 128.9, 129.0, 129.5, 135.7, 139.6, 147.1, 160.1, 173.3; m/z calculated for $C_{27}H_{26}N_2O_2$: 411.2073 (MH^+), found 411.2080 (MH^+). A white crystalline solid (Amide: 1.47 g; 26%): mp 120-123 °C; R_f 0.62 (E); R_f 0.16 (H); ν_{max} (KBr): 3059, 1620, 1235 cm^{-1}; m/z (CI): 576.2, 379.2, 198.0, 183.9, 155.9, 90.9; δ_H ($CDCl_3$, 200 MHz): 2.78 (1 H, d, J = 15.6), 3.53 (2 H, d, J = 13.6), 3.70 (2 H, d, J = 13.4), 3.86 (1 H, t, J = 11.4), 4.10 (1 H, d, J = 15.0), 4.51 (1 H, d, J = 17.2), 4.99 (2 H, t, J = 14.8), 5.34 (1 H, d, J = 17.0), 6.93 (4 H, s), 7.05-7.63 (18 H, m), 7.91 (1 H, d, J = 8.2), 8.13 (1 H, d, J = 8.6); δ_C ($CDCl_3$, 126 MHz): 28.2, 48.3, 50.6, 54.4, 61.4, 122.9, 126.0, 126.8, 126.9, 127.0, 127.5, 127.6, 127.7, 128.3, 128.8, 129.4, 135.8, 137.3, 137.6, 139.8, 146.9, 161.0, 173.0; m/z calculated for $C_{40}H_{37}N_3O$: 576.3015 (MH^+), found 576.2987 (MH^+).

N-(α-Methylbenzyl)-3Amino-3-(Quinolin-2-yl)propionic Acid Methyl Ester

To a stirred solution of α-methylbenzylamine (2.43 g; 20.0 mmol) and triethylamine (2.86 g; 28.3 mmol) in dry THF (30 mL) at room temperature under argon was added drop-wise trimethylsilyl chloride (2.39 g; 23.6 mmol). The mixture was allowed to stir at room temperature for 1 h after which triethylamine hydrochloride was removed *via* filtration under a blanket of argon. The resulting clear silylamine, in dry THF, was cooled to –78 °C and *n*-butyl lithium (1.6 M in hexanes; 9.4 mL; 15.0 mmol) was added drop-wise and the mixture stirred for 15 min. To this solution was added drop-wise 3-(quinolin-2-yl)acrylic acid methyl ester (2.13 g; 10.0 mmol) in dry THF (5 mL).

The resulting mixture was stirred at –78 °C for 15 min before quenching with saturated ammonium chloride solution (7.2 mL). The reaction mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 25 mL). The combined organic layers were concentrated under reduced pressure, after which 1 N hydrochloric acid (15 mL) was added. The resulting mixture was washed with Et_2O (3 x 25 mL) and the organic layers discarded. The aqueous layer was basified with solid potassium carbonate and extracted with DCM (4 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a red oil. Purification by column chromatography using EtOAc:hexanes (1:2) as the eluent gave an amber oil (2.32 g; 70%): R_f 0.31 (C); R_f 0.48 (K); ν_{max} (nujol): 3449, 3332, 1953, 1736, 1264, 1166, 833, 759 cm^{-1}; m/z (EI): 335.2, 319.2, 303.2, 215.0, 181.9, 156.0, 127.8, 104.9, 76.9; δ_H ($CDCl_3$, 400 MHz): 1.43 (3 H, d, J = 6.5), 2.95 (2 H, d, J = 6.3 and 2.6), 3.65 (3 H, s), 3.84 (1 H, q, J = 6.5), 4.43 (1 H, t, J = 6.6), 7.18-7.32 (6 H, m), 7.41 (1 H, d, J = 8.4), 7.51 (1 H, t J = 7.1), 7.69 (1 H, t, J = 7.0), 7.78 (1 H, d, J = 7.1), 8.05 (2 H, d, J = 8.3); δ_C ($CDCl_3$, 101 MHz): 23.7, 40.4, 51.9, 56.0, 58.6, 120.8, 126.4, 127.1, 127.1, 127.2, 127.7, 127.8, 128.6, 128.6, 129.6, 136.5, 146.0, 148.0, 162.8, 172.8; m/z calculated for $C_{21}H_{22}N_2O_2$: 335.1760 (MH^+), found 335.1766 (MH^+).

N-(α-Methylbenzyl)-3-Amino-3-(Quinolin-2-yl)propionic Acid t-Butyl Ester

To a stirred solution of α-methylbenzylamine (0.728 g; 6.00 mmol) and triethylamine (0.857 g; 8.57 mmol) in dry THF (10 mL) at room temperature under argon was added drop-wise trimethylsilyl chloride (0.717 g; 7.07 mmol). The mixture was allowed to stir at room temperature for 1 h after which triethylamine hydrochloride was removed *via* filtration under a blanket of argon. The resulting clear silylamine, in dry THF, was cooled to –78 °C and *n*-butyl lithium (1.6 M in hexanes; 2.82 mL; 4.50 mmol) was added drop-wise and the mixture stirred for 15 min. To this solution was added drop-wise 3-(quinolin-2-yl)acrylic acid *t*-butyl ester (0.774 g; 3.03 mmol) in dry THF (2 mL). The resulting mixture was stirred at –78 °C for 15 min before quenching with saturated ammonium chloride solution (2.5 mL). The reaction mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 25 mL). The combined organic layers were concentrated under reduced pressure, after which 1 N hydrochloric acid (10 mL) was added. The resulting mixture was washed with Et_2O (3 x 25 mL) and the organic layers

discarded. The aqueous layer was basified with solid potassium carbonate and extracted with DCM (4 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a red oil. Purification by column chromatography using EtOAc:hexanes (1:2) as the eluent gave an amber oil (0.58 g; 50%): R_f 0.43 (C); R_f 0.66 (D); ν_{max} (nujol): 3431, 3331, 1952, 1727, 1259, 1153, 835, 758 cm^{-1}; m/z (EI): 377.3, 321.3, 257.2, 201.1, 127.9, 105.2, 156.1; δ_H ($CDCl_3$, 200 MHz): 1.30 (1 H, d, J = 6.6), 1.35 (3 H, s), 1.38 (6 H, s), 1.43 (2 H, d, J = 6.6), 2.70 (0.7 H, d, J = 7.0), 2.81 (1.3 H, d, J = 6.8), 3.52 (0.3 H, q, J = 6.0), 3.81 (0.7 H, q, J = 6.6), 4.10 (0.3 H, t, J = 7.2), 4.40 (0.7 H, t, J = 7.0), 7.25-7.38 (5 H, m), 7.39 (1 H, d, J = 8.8), 7.50 (1 H, m), 7.68 (1 H, m), 7.78 (1 H, dd, J = 8.4 and 1.8), 8.03 (1 H, d, J = 8.4); δ_C ($CDCl_3$, 126 MHz): 29.5, 43.2, 57.2, 60.2, 121.7, 122.3, 127.5, 128.3, 128.5, 128.8, 128.9, 129.7, 129.8, 130.6, 130.7, 137.7, 149.1, 172.2; m/z calculated for $C_{24}H_{28}N_2O_2$: 377.2229 (MH^+), found 377.2235 (MH^+).

N-(α-Methylbenzyl)-3Amino-3-(Quinolin-2-yl)propionic Acid

To a stirred solution of *N*-(α-methylbenzyl)-3-amino-3-(quinolin-2-yl)propionic acid *t*-butyl ester (0.72 g; 1.9 mmol) in DCM (6 mL) was added drop-wise trifluoroacetic acid (5 mL). The reaction mixture was allowed to stir at room temperature overnight after which it was concentrated under reduced pressure to give a brown solid. The solid was dissolved in EtOAc (50 mL) and the resulting solution was washed with saturated sodium bicarbonate solution (3 x 10 mL), dried over sodium sulfate and concentrated under reduced pressure to give a rusty coloured solid. Purification by column chromatography using chloroform:MeOH (4:1) as the eluent gave a tan crystalline solid (0.50 g; 83%): mp 84 °C (decomposition); R_f 0.68 (B); R_f 0.34 (N); ν_{max} (nujol): 3443, 1686, 1602, 1421, 1132, 833, 761, 701 cm^{-1}; m/z (FAB): 321.3, 156.1, 128.1, 105.0; δ_H ($CDCl_3$, 500 MHz): 1.72 (3 H, d, J = 6.5), 2.96 (2 H, s), 4.33 (1 H, d, J = 6.4), 4.87 (1 H, s), 7.10 (3 H, s), 7.29 (3 H, d, J = 5.7), 7.53 (1 H, t, J = 7.4), 7.69 (1 H, t, J = 7.6), 7.74 (1 H, d, J = 8.0), 7.97 (1 H, d, J = 8.3), 8.02 (1 H, d, J = 8.3); δ_C ($CDCl_3$, 126 MHz): 19.8, 39.9, 58.9, 59.1, 115.6, 118.5, 119.8, 127.5, 127.8, 127.9, 128.0, 129.1, 129.2, 129.6, 130.6, 138.4, 146.8, 155.4; m/z calculated for $C_{20}H_{20}N_2O_2$: 321.1602 (MH^+), found 321.1603 (MH^+).

3-Amino-3-(Quinolin-2-yl)propionic Acid t-Butyl Ester

A solution of *N*-(α-methylbenzyl)-3-amino-3-(quinolin-2-yl)propionic acid *t*-butyl ester (0.57 g; 1.5 mmol) in 1,4-cyclohexadiene (1.4 mL) and glacial acetic acid (5.5 mL) was treated with 10% palladium on carbon (0.437 g). This mixture was allowed to stir at 75 °C under argon until completion, as determined by TLC. The reaction mixture was then allowed to cool to room temperature and filtered through Celite®. The filtrate was concentrated under reduced pressure to give a yellow oil. Trituration with Et_2O (25 mL) gave an off-white solid (36.2 mg; 9%): mp 181-183 °C; R_f 0.45 (A); R_f 0.70 (B); ν_{max} (KBr): 3438, 1727, 1598, 1272, 1157 cm^{-1}; m/z (EI): 216.0, 199.0, 182.0, 171.0, 156.9, 129.0, 101.9, 89.1; δ_H ($CDCl_3$, 400 MHz): 1.30 (9 H, s), 3.29 (2 H, d, J = 2.8), 5.16 (1 H, s), 7.55 (2 H, q, J = 7.5), 7.68 (1 H, t, J = 7.3), 7.78 (1 H, d, J = 8.0), 8.06 (1 H, d, J = 8.4), 8.13 (1 H, d, J = 8.3); δ_C ($CDCl_3$, 101 MHz): 28.2, 39.0, 52.0, 82.5, 119.8, 127.5, 127.9, 128.0, 129.6, 130.4, 138.0, 147.1, 154.6, 169.4.

N-(α-Methylbenzyl)-3-Amino-3-(Quinolin-3-yl)propionic Acid Methyl Ester

To a stirred solution of α-methylbenzylamine (1.69 g; 14.0 mmol) and triethylamine (2.03 g; 20.0 mmol) in dry THF (30 mL) at room temperature under argon was added drop-wise trimethylsilyl chloride (1.79 g; 16.5 mmol). The mixture was allowed to stir at room temperature for 1 h after which triethylamine hydrochloride was removed *via* filtration under a blanket of argon. The resulting clear silylamine, in dry THF, was cooled to −78 °C and *n*-butyl lithium (1.6 M in Hexanes; 6.56 mL; 10.5 mmol) was added drop-wise and the mixture stirred for 15 min. To this solution was added drop-wise 3-(quinolin-3-yl)acrylic acid methyl ester (1.50 g; 7.05 mmol) in a mixture of dry THF (20 mL) and toluene (1 mL). The resulting mixture was stirred at −78 °C for 15 min before quenching with saturated ammonium chloride solution (5 mL). The reaction mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 25 mL). The combined organic layers were concentrated under reduced pressure, after which 1 N hydrochloric acid (10 mL) was added. The resulting mixture was washed with Et_2O (3 x 25 mL) and the organic layers discarded. The aqueous layer was basified with solid potassium carbonate and extracted with DCM (4 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a red oil. Purification by column chromatography using gradient elution with EtOAc:hexanes (1:2,

2:1 and 3:1) gave an amber oil (1.01 g; 43%): R_f 0.08 (C); R_f 0.34 (D); ν_{max} (nujol): 3449, 3327, 1956, 1735, 1266, 1168, 788 cm^{-1}; m/z (EI): 335.3, 319.3, 261.2, 229.1, 214.0, 1556.9, 104.9; δ_H ($CDCl_3$, 400 MHz): 1.42 (3 H, d, J = 6.0), 2.85 (2 H, qd, J = 16.0 and 8.0), 3.60 (3 H, s), 3.75 (1 H, q, J = 6.0), 4.40 (1 H, t, J = 6.0), 7.11-7.19 (1 H, m), 7.23 (5 H, d, J = 6.0), 7.52 (1 H, t, J = 8.0), 7.68 (1 H, t, J = 8.0), 7.76 (1 H, d, J = 8.0), 8.03 (1 H, s), 8.09 (1 H, d, J = 8.0), 8.85 (1 H, s); δ_C ($CDCl_3$, 101 MHz): 22.7, 41.6, 51.6, 54.9, 55.3, 126.4, 126.5, 126.6, 126.9, 127.6, 127.7, 128.3, 128.5, 129.0, 133.7, 135.3, 145.2, 147.5, 150.4, 171.6; m/z calculated for $C_{21}H_{22}N_2O_2$: 334.1683 (M^+), found 334.1682 (M^+).

N-(α-Methylbenzyl)-3-Amino-3-(Isoquin-4-yl)propionic Acid Methyl Ester and N-(α-Methylbenzyl)- 3-(Isoquin-4-yl)-Acrylic Amide

To a stirred solution of α-methylbenzylamine (1.21 g; 10.0 mmol) and triethylamine (1.44 g; 14.3 mmol) in dry THF (20 mL) at room temperature under argon was added drop-wise trimethylsilyl chloride (1.28 g; 11.8 mmol). The mixture was allowed to stir at room temperature for 1 h after which triethylamine hydrochloride was removed *via* filtration under a blanket of argon. The resulting clear silylamine, in dry THF, was cooled to –78 °C and *n*-butyl lithium (1.6 M in hexanes; 4.69 mL; 7.50 mmol) was added drop-wise and the mixture stirred for 15 min. To this solution was added drop-wise 3-(isoquin4-yl)acrylic acid methyl ester (1.07 g; 5.00 mmol) in dry THF (6 mL). The resulting mixture was stirred at –78 °C for 15 min before quenching with saturated ammonium chloride solution (6 mL). The reaction mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 25 mL). The combined organic layers were concentrated under reduced pressure, after which 1 N hydrochloric acid (10 mL) was added. The resulting mixture was washed with Et_2O (3 x 25 mL) and the organic layers discarded. The aqueous layer was made basic with solid potassium carbonate and extracted with DCM (4 x 25 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a red oil. Purification by column chromatography using gradient elution with EtOAc:Hexanes (2:1, 3:1, 8:1, 10:1) as the eluent gave a yellow solid, which was recrystallized to give an off-white crystalline solid (Amide: 157 mg; 10%): mp 202-204 °C; R_f 0.17 (D); R_f 0.49 (I); ν_{max} (KBr): 3268, 3056, 1653, 1619, 1546, 974, 751 cm^{-1}; m/z (EI): 302.3, 197.0, 182.0, 128.1, 153.8, 128.1, 120.0, 104.7, 76.9; δ_H ($CDCl_3$, 200 MHz): 1.62 (3 H, d, J = 7.0), 5.33 (1 H, quin, J = 7.4),

6.62 (1 H, d, J = 15.2), 6.82 (1 H, d, J = 7.8), 7.27-7.45 (5 H, m), 7.63 (1 H, ddd, J = 9.0, 6.8 and 1.2), 7.75 (1 H, ddd, J =9.8, 7.0 and 1.6), 7.95 (1 H, dd, J = 7.8 and 1.0), 8.13 (1 H, d, J = 8.6), 8.32 (1 H, d, J = 15.6), 8.71 (1 H, s), 9.04 (1 H, s); δ_C ($CDCl_3$, 126 MHz): 21.7, 49.1, 122.8, 125.3, 126.4, 126.7, 127.4, 127.6, 128.1, 128.1, 128.7, 131.2, 133.8, 135.0, 140.6, 143.1, 153.2, 164.3; m/z calculated for $C_{20}H_{18}N_2O$: 302.1419 (M^+), found 302.1413 (M^+). Concentration of the filtrate under reduced pressure gave an amber oil (Crude Ester: 77.1 mg; 5%): R_f 0.05 (C); R_f 0.49 (I); ν_{max} (nujol): 3323, 1733, 1674, 1272, 904, 757 cm^{-1}; m/z (EI): 334.2, 319.1, 228.9, 212.9, 182.5, 153.8, 119.7, 104.8, 76.8; δ_H ($CDCl_3$, 200 MHz): 1.38 (3 H, d, J = 6.2), 2.90 (2 H, dd, J = 7.6 and 6.4), 3.63 (3 H, s), 3.78 (1 H, q, J = 6.4), 4.94 (1 H, dd, J = 8.0 and 6.0), 7.21 (5 H, s), 7.58-7.72 (2 H, m), 7.96 (1 H, dd, J = 7.4 and 0.6), 8.12 (1 H, d, J = 8.6), 8.54 (1 H, s), 9.12 (1 H, s); δ_C ($CDCl_3$, 126 MHz): 22.7, 41.5, 51.6, 52.5, 55.6, 122.5, 126.6, 126.8, 126.9, 127.1, 127.8, 128.0, 128.3, 128.4, 130.4, 131.4, 133.9, 141.6, 145.1, 152.3, 171.9.

N-(-α-Methylbenzyl)-3-Amino-3-(Benzo[d]furan-2-yl)propionic Acid Methyl Ester

To a stirred solution of α-methylbenzylamine (2.91 g; 24.0 mmol) and triethylamine (3.47 g; 34.3 mmol) in dry THF (30 mL) at room temperature under argon was added drop-wise trimethylsilyl chloride (3.06 g; 28.3 mmol). The mixture was allowed to stir at room temperature for 1 h after which triethylamine hydrochloride was removed *via* filtration under a blanket of argon. The resulting clear silylamine, in dry THF, was cooled to –78 °C and *n*-butyl lithium (1.6 M in Hexanes; 11.3 mL; 18.0 mmol) was added drop-wise and the mixture stirred for 15 min. To this solution was added drop-wise 3-(benzo[d]furan-2-yl)acrylic acid methyl ester (2.43 g; 12.0 mmol) in dry THF (7 mL). The resulting mixture was stirred at –78 °C for 15 min before quenching with saturated ammonium chloride solution (12 mL). The reaction mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 25 mL). The combined organic layers were concentrated under reduced pressure, after which 1 N hydrochloric acid (12 mL) was added. The resulting pale yellow precipitate was removed *via* filtration, dissolved in DCM (75 mL) and washed with saturated sodium bicarbonate solution (4 x 25 mL), saturated sodium chloride solution (4 x 25 mL) and water (4 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give an amber oil. Purification by column chromatography using EtOAc:hexanes (1:2) as the

eluent gave a yellow oil (1.23 g; 32%): R_f 0.71 (D); R_f 0.51 (E); ν_{max} (nujol): 3331, 1740, 1255, 1132, 809, 756 cm^{-1}; m/z (EI): 323.2, 308.2, 250.1, 218.0, 204.1, 160.9, 104.8, 76.9; δ_H ($CDCl_3$, 200 MHz): 1.40 (3 H, d, J = 6.4), 2.89 (2 H, d, J = 6.8), 3.68 (3 H, s), 3.83 (1 H, q, J = 6.2), 6.57 (1 H, s), 7.18-7.31 (7 H, m), 7.42-7.46 (1 H, m), 7.50-7.55 (1 H, m); δ_C ($CDCl_3$, 101 MHz): 23.4, 39.6, 51.3, 52.0, 55.5, 103.8, 111.5, 121.2, 123.0, 123.1, 124.3, 126.9, 127.2, 127.4, 128.6, 128.7, 145.9, 155.1, 158.4, 172.0; m/z calculated for $C_{20}H_{21}NO_3$: 323.1521 (M^+), found 323.1512 (M^+).

N-(-α-Methylbenzyl)-N'(benzenesulfonyl)-3-(2-methylindol-5-yl)propionic Acid Methyl Ester and N-(-α-Methylbenzyl)-N'(benzenesulfonyl)-3-(2-methylindol-5-yl)acrylic Amide

To a stirred solution of α-methylbenzylamine (0.911 g; 7.50 mmol) and triethylamine (1.07 g; 10.6 mmol) in dry THF (15 mL) at room temperature under argon was added drop-wise trimethylsilyl chloride (0.896 g; 8.85 mmol). The mixture was allowed to stir at room temperature for 1 h after which triethylamine hydrochloride was removed *via* filtration under a blanket of argon. The resulting clear silylamine, in dry THF, was cooled to –78 °C and *n*-butyl lithium (1.6 M in Hexanes; 3.53 mL; 5.62 mmol) was added drop-wise and the mixture stirred for 15 min. To this solution was added drop-wise *N*-(benzenesulfonyl)-3-(2-methylindol-5-yl)acrylic acid methyl ester (1.33g; 3.75 mmol) in dry THF (6 mL). The resulting mixture was stirred at –78 °C for 1 h before quenching with saturated ammonium chloride solution (10 mL). The reaction mixture was allowed to warm to room temperature and extracted with Et_2O (3 x 25 mL). The combined organic layers were concentrated under reduced pressure, after which 1 N hydrochloric acid (10 mL) was added. The resulting pale orange precipitate was removed *via* filtration, dissolved in DCM (50 mL) and washed with saturated sodium bicarbonate solution (4 x 15 mL), saturated sodium chloride solution (4 x 15 mL) and water (4 x 15 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give an amber oil. Purification by column chromatography using EtOAc:hexanes (1:2) as the eluent gave two products: a yellow oil (Ester: 0.529 g; 30%): R_f 0.15 (C); R_f 0.68 (I); ν_{max} (nujol): 3330, 1735, 1459, 1374, 1165, 1094, 888, 817, 727 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.36 (3 H, d, J = 6.5), 2.60 (3 H, d, J = 0.9), 3.60 (3 H, s), 3.68 (1 H, q, J = 8.0), 4.27 (1 H, t, J = 8.0), 7.18-7.29 (m, 6 H), 7.33 (1 H, s), 7.45 (2 H, t, J = 7.36), 7.56 (1 H, tt, J = 4.8 and 1.6), 7.80 (2 H, dd, J = 8.2 and 1.0), 8.08 (1 H, d, J =

8.6); δ_C ($CDCl_3$, 101 MHz): 16.0, 22.6, 42.8, 51.8, 55.0, 57.1, 109.9, 114.8, 123.1, 126.7, 126.7, 126.9, 126.9, 127.2, 128.7, 128.7, 129.6, 129.6, 130.1, 130.1, 134.0, 134.0, 136.6, 138.0, 139.6; m/z calculated for $C_{27}H_{28}N_2O_4S$: 476.1770 (M^+), found 476.1765 (M^+) and a yellow crystalline solid (Amide: 0.248 g; 15%): mp: 84-86 °C; R_f 0.08 (C); R_f 0.68 (I); ν_{max} (KBr): 3272, 3060, 1733, 1658, 1536, 1367, 1170, 982, 636 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.56 (3 H, d, J = 6.9), 2.57 (3 H, d, J = 0.9), 5.28 (1 H, quin, J = 7.2), 6.15 (1 H, d, J = 7.9), 6.30 (1 H, s), 6.43 (1 H, d, J = 15.6), 7.26-7.44 (8 H, m), 7.47 (1 H, s), 7.54 (1 H, tt, J = 7.5 and 1.0), 7.76 (2 H, dd, J = 8.3 and 1.0), 8.12 (1 H, d, J = 8.7); δ_C ($CDCl_3$, 101 MHz): 16.0, 22.1, 49.2, 110.0, 115.0, 120.2, 120.5, 123.4, 126.6, 126.6, 127.7, 129.0, 129.0, 129.7, 129.7, 130.3, 130.8, 134.2, 138.0, 139.4, 141.6, 143.5, 165.6; m/z calculated for $C_{26}H_{24}N_2O_3S$: 444.1508 (M^+), found 444.1513 (M^+).

N-(Benzenesulfonyl)-3-(Indol-5-yl)acrylic Acid Methyl Ester

To a solution of 3-(indol-5-yl)-acrylic acid methyl ester (1.03 g; 5.12 mmol) in dry THF (18 mL) at –78 °C under argon was added drop-wise lithium diisopropylamide, prepared from diisopropylamine (0.529 g; 5.23 mmol) and *n*-butyl lithium (1.6 M in hexanes; 3.24 mL; 5.12 mmol) in dry THF (2 mL) at –78 °C under argon. The resulting mixture was stirred for 25 min at –78 °C and then quenched with benzenesulfonyl chloride (0.950 g; 5.38 mmol). Upon cooling to room temperature overnight the reaction mixture was cooled to 5 °C, poured into 2% (w/v) sodium bicarbonate solution (50 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with 3% (w/v) sodium thiosulfate solution (3 x 25 mL), distilled water (3 x 20 mL) and saturated sodium chloride solution (3 x 25 mL), dried over sodium sulfate and concentrated under reduced pressure to give a yellow solid. Purification by column chromatography with Et_2O:hexanes (2:1) as the eluent afforded a yellow powder (1.26 g; 72%): mp 134-136 °C; R_f 0.37 (J); R_f 0.79 (E); ν_{max} (KBr): 3123, 1717, 1637, 1365, 1308, 1176, 1115; m/z (EI): 341.2, 310.2, 200.1, 185.0, 169.0, 140.9, 115.0, 77.1; δ_H ($CDCl_3$, 200 MHz): 3.79 (3 H, s), 6.41 (1 H, d, J = 16.0), 6.67 (1 H, dd, J = 3.6 and 0.6), 7.40-7.54 (4 H, m), 7.59 (1 H, d, J = 3.8), 7.66 (1 H, d, J = 1.4), 7.74 (1 H, d, J = 16.0), 7.88 (2 H, dd, J = 8.2 and 1.8), 7.99 (1 H, d, J = 8.4); δ_C ($CDCl_3$, 126 MHz): 51.5, 109.2, 113.8, 117.0, 121.8, 124.1,

126.7, 127.3, 129.3, 129.8, 131.1, 134.0, 135.7, 138.0, 144.8, 167.4; m/z calculated for $C_{18}H_{15}O_4NS$: 341.0722 (M^+), found 341.0718 (M^+).

N-(Benzenesulfonyl)-3-(2-Methylindol-5-yl)acrylic Acid Methyl Ester

To a solution of 3-(2-methylindol-5-yl)-acrylic acid methyl ester (1.10 g; 5.12 mmol) in dry THF (20 mL) at –78 °C under argon was added drop-wise lithium diisopropylamide, prepared from diisopropylamine (0.529 g; 5.23 mmol) and *n*-butyl lithium (1.6 M in hexanes; 3.24 mL; 5.12 mmol) in dry THF (2 mL) at –78 °C under argon. The resulting mixture was stirred for 25 min at –78 °C and then quenched with benzenesulfonyl chloride (0.950 g; 5.38 mmol). Upon cooling to room temperature overnight the reaction mixture was cooled to 5 °C, poured into 2% (w/v) sodium bicarbonate solution (50 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with 3% (w/v) sodium thiosulfate solution (3 x 25 mL), distilled water (3 x 20 mL) and saturated sodium chloride solution (3 x 25 mL), dried over sodium sulfate and concentrated under reduced pressure to give a tan solid. Purification by column chromatography with DCM as the eluent afforded a white powder (1.57 g; 86%): mp 126-128 °C; R_f 0.39 (C); R_f 0.72 (E); ν_{max} (KBr): 1725, 1635, 1367, 1281, 1242, 1169, 994, 640; m/z (EI): 355.3, 214.2, 199.0, 182.0, 153.8, 140.8; δ_H ($CDCl_3$, 400 MHz): 2.60 (3 H, s), 3.81 (3 H, s), 6.37 (1 H, s), 6.43 (1 H, d, J = 16.0), 7.43 (1 H, d, J = 1.7), 7.45 (2 H, d, J = 8.0), 7.56 (2 H, tt, J = 7.5, 1.2), 7.75 (1 H, d, J = 16.3), 7.79 (2 H, dd, J = 8.4, 1.1), 8.17 (1 H, d, J = 8.7); δ_C ($CDCl_3$, 101 MHz): 16.0, 52.0, 109.0, 115.1, 117.1, 120.7, 123.8, 126.6, 129.7, 130.2, 130.4, 134.2, 138.4, 138.9, 139.4, 145.4, 167.9; m/z calculated for $C_{19}H_{17}NO_4S$: 355.0878 (M^+), found 355.0875 (M^+).

N-(t-Butyldimethylsilyl)-5-Bromo-2-Methylindole

To a solution of 5-bromo-2-methylindole (0.999 g; 4.76 mmol) in dry THF (50 mL) at room temperature under argon was added portion wise sodium hydride as a 60% dispersion in mineral oil (0.213 g; 5.33 mmol). The resulting mixture was stirred for 40 min at room temperature under argon and then quenched with *t*-butyldimethylsilyl chloride (1.0 M in THF; 5.6 mL; 5.6 mmol). After 4 h, saturated ammonium chloride (50 mL) was added and the mixture extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with saturated sodium chloride (3 x 50 mL), dried over sodium

sulfate and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography with EtOAc:hexanes (1:9) as the eluent followed by recrystallization with EtOH gave pale yellow crystals (1.15 g; 74%): mp 82-84 °C; R_f 0.60 (C); R_f 0.10 (G); ν_{max} (KBr): 2956, 1566, 1454, 1258, 1048, 806; m/z (ES): 324.3, 245.3, 129.0, 115.1; δ_H ($CDCl_3$, 400 MHz): 0.67 (6 H, s), 0.96 (9 H, s), 2.49 (3 H, s), 6.28 (1 H, s), 7.14 (1 H, dd, J = 8.9 and 2.1), 7.36 (1 H, d, J = 8.9), 7.60 (1 H, d, J = 2.1); δ_C ($CDCl_3$, 101 MHz): -0.2, 17.9, 20.9, 27.0, 105.9, 113.3, 115.7, 121.9, 123.3, 133.5, 141.6, 143.9; m/z calculated for $C_{15}H_{22}NSiBr$: 323.0705 (M^+), found 323.0703 (M^+).

N-(o-Methoxyphenyl)quinoline-2-Carboximine

A mixture of quinoline-2-carboxaldehyde (3.14 g; 20.0 mmol) and *o*-anisidine (2.46 g; 20.0 mmol) in DCM (30 mL) was allowed to stir over 3 Å molecular sieves at room temperature overnight. The reaction mixture was filtered through Celite® and concentrated under reduced pressure to give an amber solid. Purification by recrystallization with EtOAc and hexanes gave a mustard powder (2.35 g; 45%): mp 109-111 °C; R_f 0.35 (C); R_f 0.45 (E); ν_{max} (KBr): 3422, 1587, 1242, 1023, 746; m/z (EI): 262.2, 231.1, 154.7, 27.9, 91.7, 76.9; δ_H ($CDCl_3$, 400 MHz): 3.93 (3 H, s), 7.00-7.04 (2 H, m), 7.19 (1 H, dd, J = 7.6 and 1.4), 7.26 (1 H, td, J = 7.9 and 1.6), 7.60 (1 H, t, J = 7.1), 7.76 (1 H, t, J = 8.3), 7.86 (1 H, d, J = 8.1), 8.17 (1 H, d, J = 8.5), 8.25 (1 H, d, J = 8.6), 8.43 (1 H, d, J = 8.6), 8.85 (1 H, s); δ_C ($CDCl_3$, 101 MHz):56.2, 112.0, 119.2, 120.9, 121.4, 128.0, 128.1, 128.1, 129.2, 130.0, 130.2, 136.9, 140.7, 148.3, 152.9, 155.3, 162.1; m/z calculated for $C_{17}H_{14}N_2O$: 262.1106 (M^+), found (M^+).

N-(o-Methoxyphenyl)-2-Chloroquinoline-3-Carboximine

A mixture of 2-chloroquinoline-3-carboxaldehyde (3.85 g; 20.0 mmol) and *o*-anisidine (2.46 g; 20.0 mmol) in DCM (30 mL) was allowed to stir over 3 Å molecular sieves at room temperature overnight. The reaction mixture was filtered through Celite® and concentrated under reduced pressure to give an amber solid. Purification by recrystallization with EtOAc and hexanes gave a bright yellow powder (4.80 g; 81%): mp 133-135 °C; R_f 0.41 (C); R_f 0.60 (E); ν_{max} (KBr): 3414, 1580, 1245, 1047, 1020; m/z (EI): 296.1, 261.1, 245.1, 231.0, 162.8, 133.9, 119.9, 91.7, 76.7; δ_H ($CDCl_3$, 400

MHz): 3.94 (3 H, s), 7.00-7.05 (2 H, s), 7.12 (1 H, dd, J = 7.6 and 1.7), 7.28 (1 H, td, J = 8.2 and 1.7), 7.60 (1 H, ddd, J = 8.1, 7.0 and 1.1), 7.80 (1 H, ddd, J = 8.4, 7.0 and 1.4), 7.96 (1 H, dt, J = 8.2 and 0.8), 8.05 (1 H, dd, J = 8.5 and 0.6), 9.09 (1 H, s), 9.03 (1 H, s); δ_C ($CDCl_3$, 101 MHz): 52.6, 111.9, 120.9, 121.5, 127.5, 127.9, 128.0, 128.1, 128.7, 129.2, 132.2, 138.2, 141.3, 148.8, 150.6, 152.8, 157.1; m/z calculated for $C_{17}H_{13}N_2OCl$: 296.7551 (M^+), found (M^+).

N-(o-Methoxyphenyl)-3-Amino-3-(Quinolin-2-yl)propionic Acid Methyl Ester

To a solution of *N*-(*o*-methoxyphenyl)quinoline-2-carboximine (0.53 g; 2.01 mmol) and methyl bromoacetate (0.74 g; 4.80 mmol) in DCM (8 mL) under argon at room temperature was added zinc-copper couple (0.54 g; 8.00 mmol). The reaction mixture was allowed to stir for 17 hr at room temperature after which it was poured into 1 N hydrochloric acid solution (30 mL). The aqueous layer was extracted with DCM (1 x 25 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2 x 25 mL), water (2 x 25 mL) and saturated sodium chloride solution (2 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give an amber oil. Purification by column chromatography using EtOAc:hexanes (1:2) as the eluent gave a pale yellow crystalline solid (0.32 g; 47%): mp 119-121 °C; R_f 0.33 (C); R_f 0.32 (E); ν_{max} (KBr): 3385, 1727, 1598, 1281, 1230, 1182, 1048, 1023, 913; m/z (EI): ; δ_H ($CDCl_3$, 400 MHz): 3.17 (2 H, ddd, J = 12.7, 7.2 and 5.9), 3.67 (3 H, s), 3.91 (3 H, s), 5.26 (1 H, t, J = 5.9), 6.60 (1 H, dd, J = 7.8 and 1.5), 6.67 (1 H, td, J = 7.7 and 1.5), 6.76 (1 H, td, J = 7.6 and 1.4), 6.80 (1 H, dd, J = 7.8 and 1.2), 7.53 (1 H, d, J = 7.1), 7.58 (1 H, d, J = 8.8), 7.74 (1 H, t, J = 8.2), 7.80 (1 H, d, J = 8.1), 8.12 (1 H, d, J = 8.5), 8.18 (1 H, d, J = 7.9); δ_C ($CDCl_3$, 101 MHz): 40.6, 52.1, 55.9, 56.1, 110.1, 111.4, 117.6, 119.8, 121.5, 126.9, 127.8, 127.9, 129.0, 130.2, 136.8, 137.9, 147.5, 162.2, 172.2; m/z calculated for $C_{20}H_{20}N_2O_3$: 336.1474 (M^+), found (M^+).

Preparation of Zinc-Copper Couple: To a vigorously stirred solution of cupric acetate monohydrate (0.3 g; 1.5 mmol) in glacial acetic acid (5 mL) at high temperature was added portion-wise zinc dust (3 g; 46 mmol). The reaction mixture was allowed to stir for 30 min after which the glacial acetic acid was decanted. The couple was washed with glacial acetic acid (1 x 10 mL), Et_2O (1 x 10 mL) and benzene (1 x 10 mL). The residue solvent was removed under a stream of argon to give a dark gray powder.

N-(o-Methoxyphenyl)-3-Amino-3-(2-Chloroquinolin-3-yl)propionic Acid Methyl Ester

To a solution of *N*-(*o*-methoxyphenyl)-2-chloroquinoline-3-carboximine (0.60 g; 2.01 mmol) and methyl bromoacetate (0.74 g; 4.80 mmol) in DCM (8 mL) under argon at room temperature was added zinc-copper couple (0.54 g; 8.00 mmol). The reaction mixture was allowed to stir for 17 hr at room temperature after which it was poured into 1 N hydrochloric acid solution (30 mL). The aqueous layer was extracted with DCM (1 x 25 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2 x 25 mL), water (2 x 25 mL) and saturated sodium chloride solution (2 x 25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a brown solid. Purification by filtration through a silica plug using EtOAc:hexanes (1:2) as the eluent gave a pale yellow crystalline solid (0.32 g; 43%): mp 135-137 °C; R_f 0.32 (C); R_f 0.55 (E); ν_{max} (KBr): 3374, 1732, 1596, 1290, 1255, 1203, 1060, 1008, 954; m/z (EI): ; δ_H ($CDCl_3$, 400 MHz): 3.15 (2 H, dd, J = 13.6 and 4.2), 3.68 (3 H, s), 3.96 (3 H, s), 5.33 (1 H, q, J = 4.2), 6.32-6.35 (1 H, m), 668-6.71 (2 H, m), 6.80-6.83 (1 H, m), 7.51 (1 H, ddd, J = 8.1, 7.0 and 1.1), 7.70 (1 H, ddd, J = 8.4, 7.0 and 1.4), 7.76 (1 H, dd, J = 8.2 and 0.9), 8.01 (1 H, d, J = 8.5), 8.29 (1 H, s); δ_C ($CDCl_3$, 101 MHz): 40.4, 52.3, 52.4, 56.0, 110.1, 112.2, 118.6, 121.5, 127.5, 127.7, 128.2, 128.4, 130.8, 133.0, 137.1, 147.4, 147.7, 149.8, 171.4; m/z calculated for $C_{20}H_{19}N_2O_3Cl$: 370.1084 (M^+), found (M^+).

Example 2 Pilocarpine Assay

A seizure model is performed using adult male Sprague-Dawley rats in accordance with the guidelines of the Canada Council on Animal Care and under the supervision of the Queen's University Animal Ethics Committee. This test procedure was adopted from previous work by Turski *et al.* (1984) *Brain Res.* 321:237. The test compounds are administered at 100mg/kg by intraperitoneal (i.p.) injection. Seizures are induced 20 minutes afterwards by i.p. administration of pilocarpine hydrochloride (350 mg/kg). Protection is defined as the absence of clonic spasms over a 30 minute observation period after pilocarpine administration.

Example 3 MES Induced Seizure Model

For the maximal electroshock seizure test (MES), corneal electrodes primed with a drop of electrolyte solution (0.9% NaCl) are applied to the eyes of the animal and an

electrical stimulus (50 mA for mice, 150 mA for rats; 60 Hz) is delivered for 0.2 second at the time of the peak effect of the test compound. The animals are restrained by hand and are released at the moment of stimulation in order to permit observation of the seizure. Abolition of hind-leg tonic-extensor component (hind-leg tonic extension does not exceed a 90° angle to the plane of the body) indicates that the compound prevents MES-induced seizure spread.

Example 4 PTZ Induced Seizure Model

In the subcutaneous pentylenetetrazole (PTZ)-induced seizure model, seizures are induced 0.5 and 4 hrs after test compound administration by i.p. injection of PTZ (85mg/kg in mice and 70 mg/kg in rats). Protection is defined as the inhibition of clonic spasms over a 30 min observation period.

Example 5 SRS Model of Epilepsy

The "spontaneous recurrent seizures" (SRS) model of epilepsy is used to evaluate candidate compounds in a model for Phase 1 epileptogenesis (see, *e.g.*, Mello, E. *et al.*, *Epilepsia* (1993) 34:985; Cavalheiro, J. *et al.*, *Epilepsia* (1991) 32:778). In the SRS model, an adult male Sprague-Dawley rat (c. 260 g) is given pilocarpine by injection (380 mg/kg i.p.). Within 25 minutes, the animal enters *status epilepticus*, which typically lasts for 15-20 hours (although about 10% of animals die at this stage). The rat is allowed to spontaneously recover and is given food and water *ad lib.* and maintained on a 12 hour/12 hour light/dusk cycle. Beginning on about day 13-15, the rats develop spontaneous recurrent seizures, which occur at the rate of about 4-5 per week. The rats are videotaped 24 hours per day, and the videotapes are reviewed for behavioral seizures (including head nodding, forelimb clonus, and rearing), which are counted. The animals are watched for three months, permitting evaluation of a sufficient number of seizures. An experimental compound for evaluation can be administered at either of two times: Time 1, on Day 1, after the cessation of *status epilepticus* but before the onset of SRS; or Time 2, on Day 30, when the rats have been experiencing SRS for about two weeks. Administration of the candidate compound at Time 1 permits evaluation for anti-epileptogenic properties (ability to prevent the onset of seizures); administration of compounds at Time 2 permits evaluation of drugs as anti-ictogenics with the ability to suppress established seizures.

As a reference, the standard anticonvulsant phenytoin was administered (20 mg/kg/day i.v. for 10 day) at either Time 1 or Time 2. As expected, phenytoin was ineffective in preventing the onset of seizures when administered at Time 1, but was 75% effective at decreasing seizure frequency by 50% or more when administered at Time 2.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. The contents of all publications cited herein are hereby incorporated by reference.

CLAIMS

1. A method for inhibiting epileptogenesis in a subject, comprising administering to said subject an effective amount of an anti-epileptogenic agent, such that said epileptogenesis in said subject is inhibited, wherein said anti-epileptogenic agent is a β-heterocyclic-β-amino acid, or a salt or ester, *N*-substituted analog, or prodrug thereof.

2. A method for treating a subject suffering from an epileptogenesis-associated condition, comprising administering to said subject an effective amount of an anti-epileptogenic agent, such that said subject is treated wherein said anti-epileptogenic agent is a β-heterocyclic-β-amino acid, or a salt or ester, *N*-substituted analog, or prodrug thereof.

3. A method for treating convulsions in a subject comprising administering to said subject an effective amount of an anti-epileptogenic agent, such that said subject is treated, wherein said anti-epileptogenic agent is a β-heterocyclic-β-amino acid, or a salt or ester, *N*-substituted analog, or prodrug thereof.

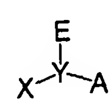
4. The method of any one of claims 1-3, wherein said subject is a mammal.

5. The method of any one of claims 1-4, wherein said subject is a human.

6. The method of claim 5, wherein said subject is suffering from head trauma, pain, stroke, anxiety, schizophrenia, multiple sclerosis, amyloid lateral sclerosis, psychoses, cerebral ischemia, Huntington's chorea, motor neuron disease, Alzheimer's disease, or dementia.

7. The method of any one of claims 1-5, wherein said subject is suffering from epilepsy.

8. A method for inhibiting epileptogenesis in a subject, comprising administering to said subject an effective amount of an anti-epileptogenic agent such that said epileptogenesis is inhibited, wherein said anti-epileptogenic agent is of the Formula:



(I)

wherein:

X is a heterocyclic moiety;

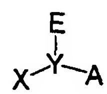
E is a hydrogen bond donor;

Y is a connecting moiety;

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

9. A method for treating a epileptogenesis-associated condition in a subject, comprising administering to said subject an effective amount of an anti-epileptogenic agent such that said subject is treated for said epileptogenesis-associated condition, wherein said anti-epileptogenic agent is of the Formula:



(I)

wherein

X is a heterocyclic moiety;

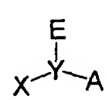
Y is a connecting moiety;

E is a hydrogen bond donor;

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

10. A method for treating convulsions in a subject, comprising administering to said subject an effective amount of an anti-epileptogenic agent such that said subject is treated for said convulsions, wherein said anti-epileptogenic agent is of the Formula:



(I)

wherein

X is a heterocyclic moiety;

Y is a connecting moiety;

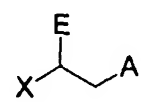
E is a hydrogen bond donor;

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

11. The method of any one of claims 8-10, wherein said connecting moiety is alkyl.

12. The method of any one of claims 8-11, wherein said anti-epileptogenic agent is of the Formula:



(II)

13. The method of any one of claims 8-12, wherein said hydrogen bond donor is NR^2R^3, OH, or SH, wherein R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl.

14. The method of claim 13, wherein said hydrogen bond donor is NR^2R^3.

15. The method of claim 14, wherein said hydrogen bond donor wherein R^2 and R^3 are each hydrogen.

16. The method of any one of claims 8-15, wherein said hydrogen bond acceptor is carboxylate, carboxylic acid, sulfate, sulfonate, sulfinate, sulfamate, phosphate, phosphonate, tetrazolyl, phosphinate, or phosphorothioate.

17. The method of claim 16, wherein said hydrogen bond acceptor is carboxylate or a carboxylic acid.

18. The method of any one of claims 8-17, wherein said heterocyclic moiety comprises a heteroaromatic group.

19. The method of claim 18, wherein said heterocyclic moiety comprises a substituted or unsubstituted monocyclic heterocycle.

20. The method of claim 19, wherein said heterocycle is thienyl, pyrrolyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl, or furanyl.

21. The method of claim 20, wherein said heterocycle is unsubstituted.

22. The method of any one of claims 8-17, wherein said heterocyclic moiety is multicyclic or polycyclic.

23. The method of claim 22, wherein said heterocyclic moiety comprises two or more bridged rings.

24. The method of claim 23, wherein at least one of said bridged rings is phenyl.

25. The method of claim 23 or 24, wherein at least one of said rings is thienyl, pyrrolyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl, or furanyl.

26. The method of claim 22, wherein said heterocyclic moiety comprises one or more fused rings.

27. The method of claim 26, wherein said heterocyclic moiety comprises one or more aromatic rings.

28. The method of claim 27, wherein said heterocyclic moiety is bicyclic.

29. The method of claim 28, wherein said heterocyclic moiety is benzothiazolonyl, indolonyl, benzooxoazolinyl, benzothiophenyl, benzofuranyl, quinolinyl, isoquinolinyl, benzodioxazolyl, benzoxazolyl, benzothiazolyl, benzoimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, indolyl, purinyl, or deazapurinyl.

30. The method of claim 29, wherein said heterocyclic moiety is indolyl, isoquinolyl, quinolinyl, benzothiazolinonyl, benzothiophenyl, benzofuranyl, methylenedioxyphenyl, or ethylenedioxyphenyl.

31. The method of claim 14, wherein said heterocyclic moiety is isooxazolylphenyl.

32. The method of any one of claims 8-30, wherein said heterocyclic moiety is substituted or unsubstituted.

33. The method of any one of claims 8-12, wherein said anti-epileptogenic agent is selected from the group consisting of:

3-(benzo[b]thiophen-3-yl)-3-aminopropionic acid;

3-(benzo[b]furan-2-yl)-3-aminopropionic acid;

3-(benzo[b]dioxolan-5-yl)-3-aminopropionic acid;

3-(quinolin-2-yl)-3-aminopropionic acid;

3-(2-chloroquinolin-3-yl)-3-aminopropionic acid;

3-(benzo[b]dioxan-6-yl)-3-aminopropionic acid;

3-(indol-4-yl)-3-aminopropionic acid;

3-(7-methylindol-4-yl)-aminopropionic acid;

3-(isoquinolin-4-yl)-3-aminopropionic acid;

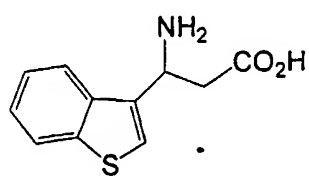
3-(quinolin-3-yl)-3-aminopropionic acid;

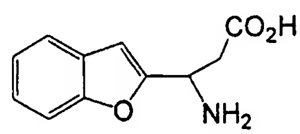
3-(benzo[b]thiazolinon-5-yl)-3-aminopropionic acid; and

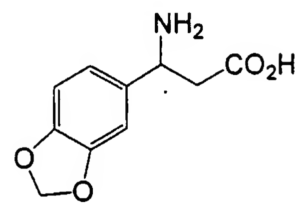
3-(4-hydroxy-3-isoxazol-5-ylphenyl)-3-aminopropionic acid

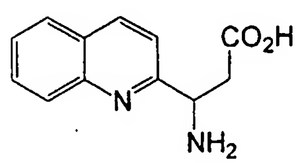
and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

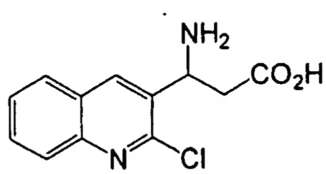
34. The method of any one of claims 8-12, wherein said anti-epileptogenic agent is selected from the group consisting of:

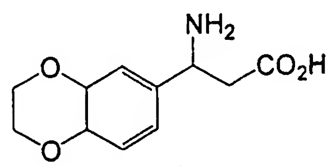


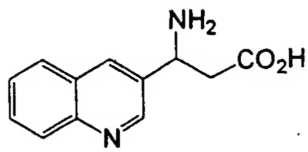


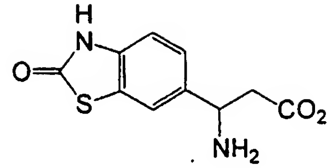


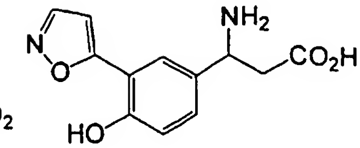


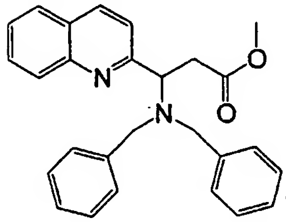


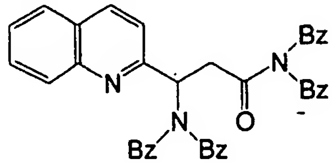


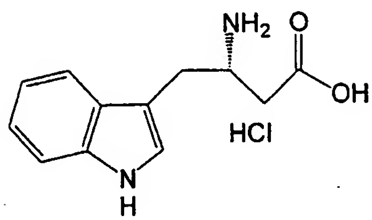


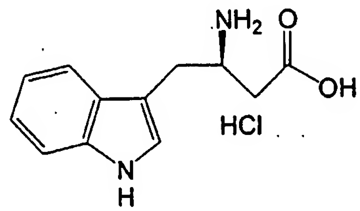


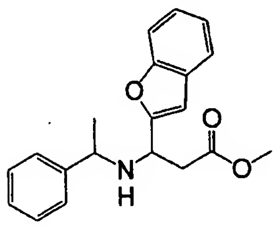


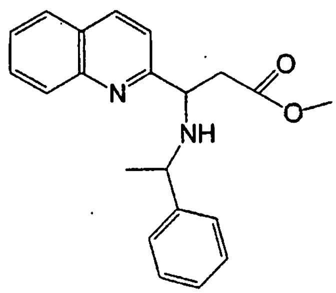


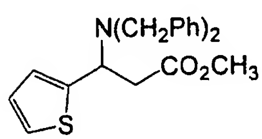


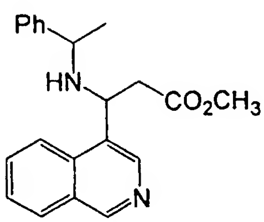


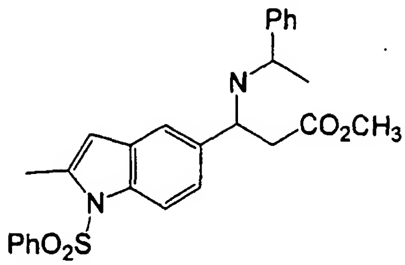


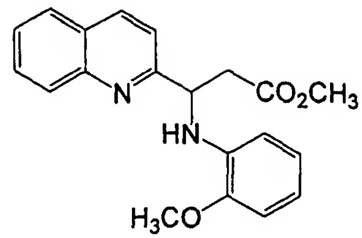


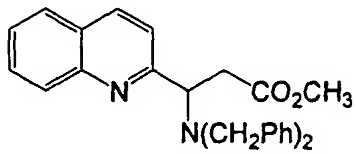


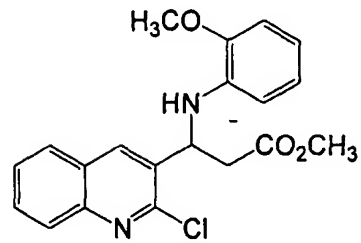












35. The method of any one of claims 1-34, wherein said anti-epileptogenic agent modulates GAT-1 or GAT-2.

36. The method of any one of claims 1-35, wherein said anti-epileptogenic agent modulates GAT-3.

37. The method of claim 35, wherein said anti-epileptogenic agent inhibits GAT-1 or GAT-2.

38. The method of claim 36 or 37, wherein said anti-epileptogenic agent inhibits GAT-3.

39. The method of any one of claims 1-38, wherein said anti-epileptogenic agent inhibits the uptake of synaptic GABA.

40. The method of any one of claims 1-39, wherein said anti-epileptogenic agent is a glutamatergic excitation modulator.

41. The method of claim 40, wherein said anti-epileptogenic agent is a glutamatergic excitation inhibitor.

42. The method of any one of claims 1-41, wherein said anti-epileptogenic agent interacts with the NMDA receptor.

43. The method of any one of claims 1-42, wherein said anti-epileptogenic agent is capable of crossing the blood brain barrier.

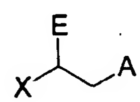
44. The method of any one of claims 1-43, wherein said anti-epileptogenic agent has a pharmaceutically acceptable neurotoxicity.

45. The method of any one of claims 2, and 4-44, wherein said epileptogenesis-associated condition is head trauma, pain, stroke, anxiety, schizophrenia, other psychoses, cerebral ischemia, Huntington's chorea, motor neuron disease, Alzheimer's disease, or dementia.

46. The method of any one of claims 2, and 4-44, wherein said epileptogenesis-associated condition is epilepsy.

47. The method of claims 8-46, wherein said anti-epileptogenic agent is administered in combination with a pharmaceutically acceptable carrier.

48. A pharmaceutical composition, comprising a therapeutically effective amount of an anti-epileptogenic agent and a pharmaceutical acceptable carrier, wherein said anti-epileptogenic agent is of the Formula:



(II)

wherein:

X is a heterocyclic moiety;

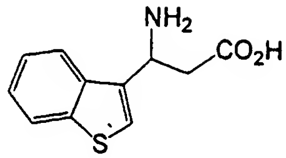
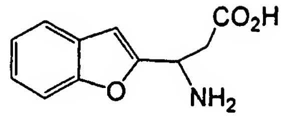
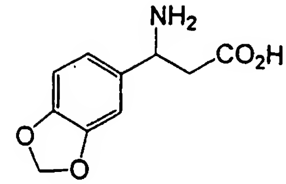
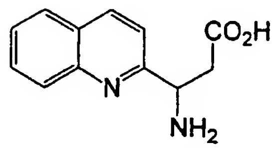
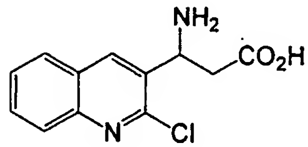
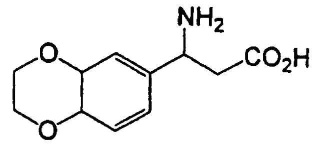
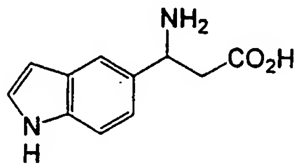
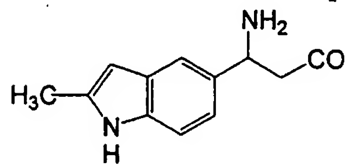
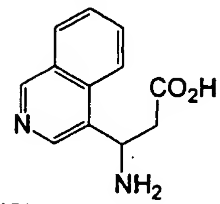
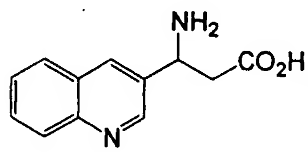
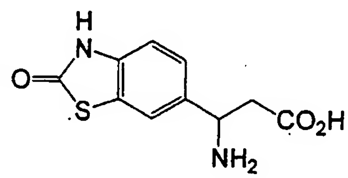
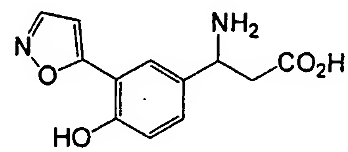
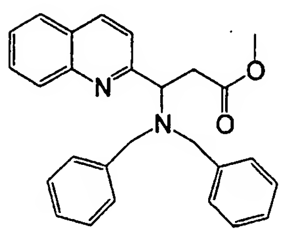
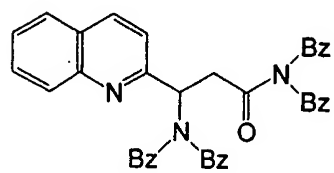
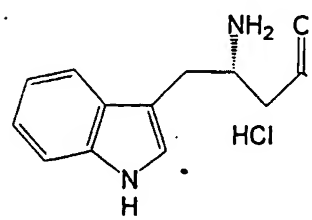
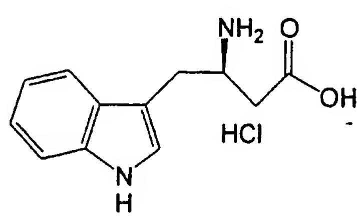
E is a hydrogen bond donor;

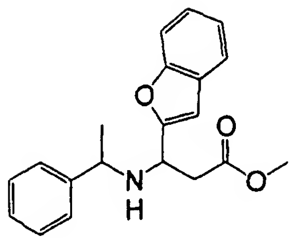
Y is a connecting moiety;

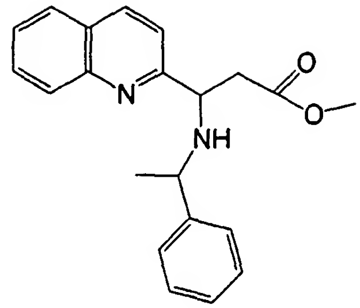
A is an hydrogen bond acceptor,

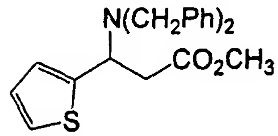
and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

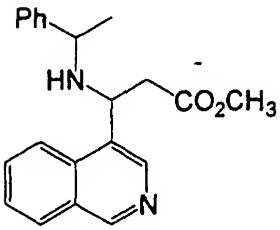
49. A pharmaceutical composition, comprising a therapeutically effective amount of an anti-epileptogenic agent and a pharmaceutical acceptable carrier, wherein said anti-epileptogenic agent is selected from the group consisting of:

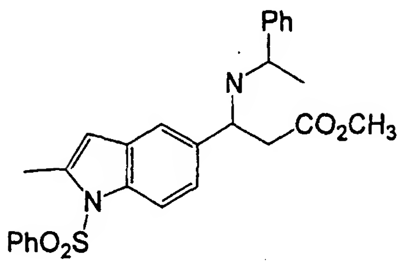

















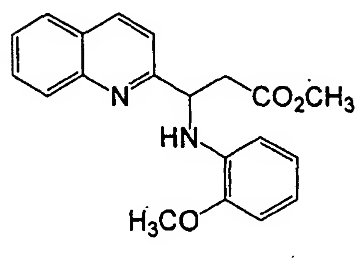


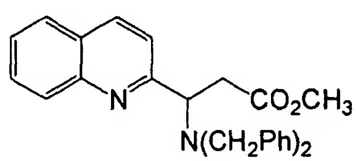


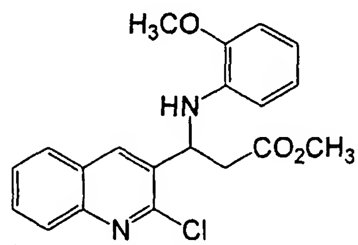












and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

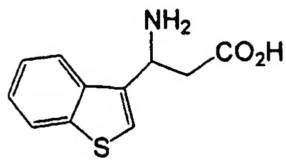
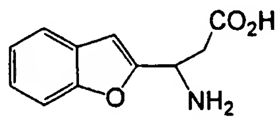
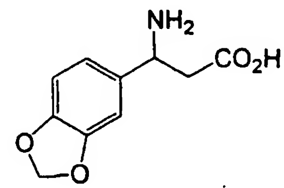
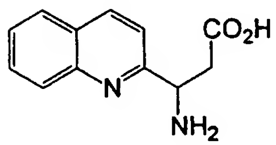
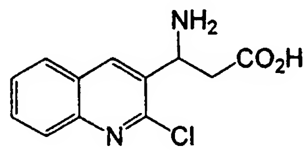
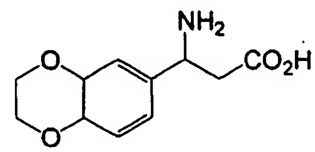
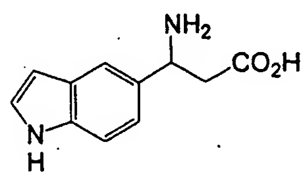
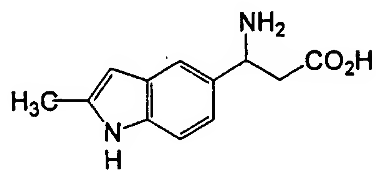
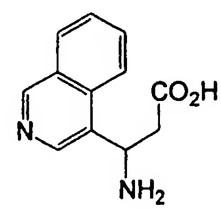
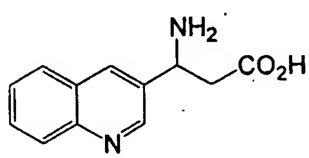
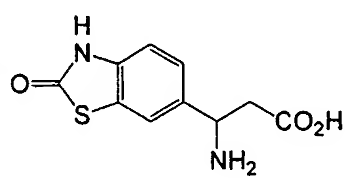
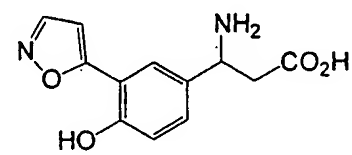
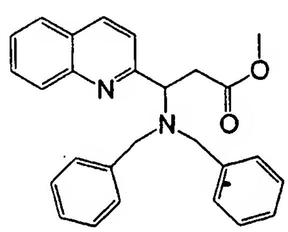
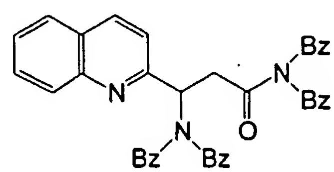
50. The pharmaceutical composition of claim 48 or 49, wherein said effective amount is effective to treat an epileptogenesis-associated state.

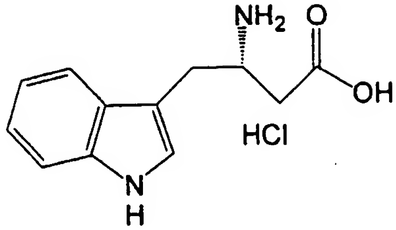
51. The pharmaceutical composition of claim 50, wherein said epileptogenesis-associated state is head trauma, pain, stroke, anxiety, schizophrenia, other

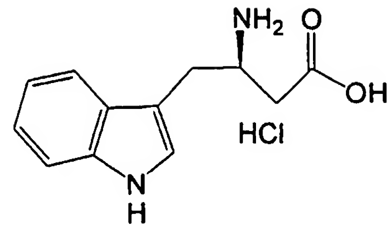
psychoses, cerebral ischemia, Huntington's chorea, motor neuron disease, Alzheimer's disease, or dementia.

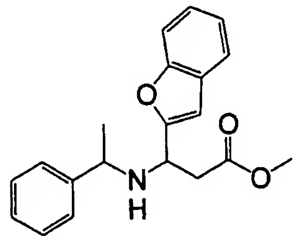
52. The pharmaceutical composition of claim 50, wherein said epileptogenesis-associated state is epilepsy.

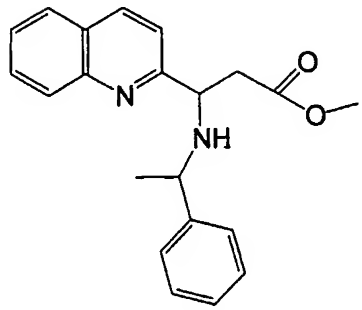
53. A compound selected from the group consisting of:

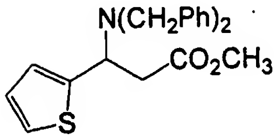















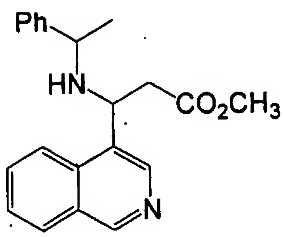


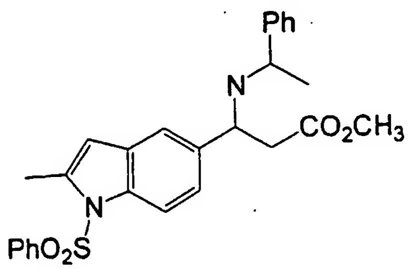


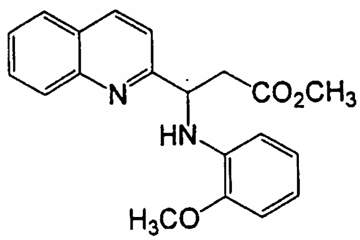


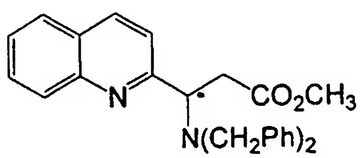


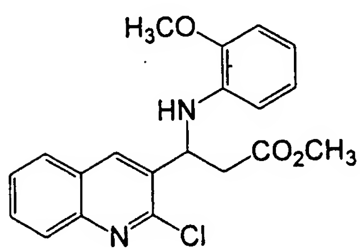






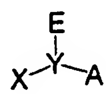






and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

54. A method of diagnosing an epileptogenesis-associated condition in a subject comprising administering an anti-epileptogenic agent, labeled with a detectable marker to said subject; and measuring increased binding of the compound to the NMDA receptors of the neurons of said subject's brain, thereby diagnosing an epileptogenesis-associated condition in said subject, wherein said anti-epileptogenic agent is a β-heterocyclic-β-amino acid or a compound of the Formula:



(I)

wherein

X is a heterocyclic moiety;

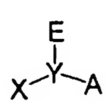
Y is a connecting moiety;

E is a hydrogen bond donor;

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

55. A method of diagnosing an epileptogenesis-associated state, comprising administering an anti-epileptogenic agent labeled with a detectable marker to a subject; and measuring decreased binding of the compound to the GABA receptors or transporters of the neurons of said subject's brain, thereby diagnosing the epileptogenesis-associated condition in said subject, wherein said anti-epileptogenic agent is a β-heterocyclic-β-amino acid or a compound of the Formula:



(I)

wherein

X is a heterocyclic moiety;

Y is a connecting moiety;

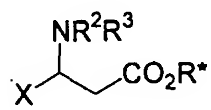
E is a hydrogen bond donor;

A is an hydrogen bond acceptor,

and pharmaceutically acceptable salts or esters, *N*-substituted analogs, and prodrugs thereof.

56. The method of any one of claims 1-35, wherein said anti-epileptogenic agent inhibits or modulates GABA transaminase.

57. A method for inhibiting epileptogenesis in a subject, comprising administering to said subject an effective amount of an anti-epileptogenic agent, such that said epileptogenesis in said subject is inhibited, wherein said anti-epileptogenic agent is of the Formula (IIa):



(IIa)

wherein:

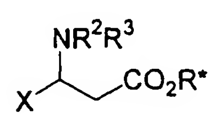
R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl;

X is a heterocyclic moiety; and

R* is a substituted or unsubstituted alkyl moiety, a substituted or unsubstituted aryl moiety, a hydrogen, or a physiologically acceptable cation;

and pharmaceutically acceptable salts and prodrugs thereof.

58. A method for treating a subject suffering from an epileptogenesis-associated disorder, comprising administering to said subject an effective amount of an anti-epileptogenic agent, such that said subject is treated wherein said anti-epileptogenic agent is of the Formula (IIa):



(IIa)

wherein:

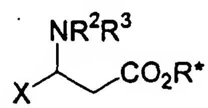
R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl;

X is a heterocyclic moiety; and

R* is a substituted or unsubstituted alkyl moiety, a substituted or unsubstituted aryl moiety, a hydrogen, or a physiologically acceptable cation;

and pharmaceutically acceptable salts and prodrugs thereof.

59. A method for treating convulsions in a subject comprising administering to said subject an effective amount of an anti-epileptogenic agent, such that said subject is treated, wherein said anti-epileptogenic agent is of the Formula (IIa):



(IIa)

wherein:

R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylaryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl;

X is a heterocyclic moiety; and

R* is a substituted or unsubstituted alkyl moiety, a substituted or unsubstituted aryl moiety, a hydrogen, or a physiologically acceptable cation;

and pharmaceutically acceptable salts and prodrugs thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 02/00773

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 A61K31/405 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, PAJ, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CARRAN JOHN R ET AL: "beta-Amino acids, a novel class of antiictogenic/antiepileptogenic agents." EPILEPSIA, vol. 39, no. SUPPL. 6, 1998, page 40 XP001095167 Annual Meeting of the American Epilepsy Society;San Diego, California, USA; December 6-9, 1998 ISSN: 0013-9580 the whole document ---	1-59
A	WO 98 40055 A (TAN CHRISTOPHER Y K ;CARRAN JOHN R (CA); UNIV KINGSTON (CA); MILNE) 17 September 1998 (1998-09-17) tables 2,3 claims 1-15 page 64; example B6P105 ---	1-59

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2002	16/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giacobbe, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JARELL ABEL D ET AL: "Antiepileptogenic agents: How close are we?" DRUGS, vol. 61, no. 8, 2001, pages 1045-1055, XP001095130 ISSN: 0012-6667 table III	6,45
X	WO 00 56715 A (ORTHO MCNEIL PHARM INC) 28 September 2000 (2000-09-28) examples 1-22	53
X	EP 0 718 280 A (ISAGRO RICERCA SRL) 26 June 1996 (1996-06-26) table 28	53
X	WO 00 06570 A (MARYANOFF BRUCE E ;LAWSON EDWARD C (US); HOEKSTRA WILLIAM J (US);) 10 February 2000 (2000-02-10) page 26; example AA4	53
X	GB 2 327 672 A (MERCK & CO INC) 3 February 1999 (1999-02-03) examples 2-2	53
X	WO 99 52493 A (TEXAS BIOTECHNOLOGY CORP) 21 October 1999 (1999-10-21) page 12; example 21	53

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 02/00773

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 54-56 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.
The same applies to claims 1-47 and 57-59, which are directed to a method of treatment of the human/animal body

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/00773

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
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			WO	9840055	A2	17-09-1998
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			EP	0843967	A1	27-05-1998
			ES	2144885	T3	16-06-2000
			GR	3033350	T3	29-09-2000
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			JP	2002511397	T	16-04-2002
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			NO	20005161	A	15-12-2000
			NO	20005162	A	15-12-2000
			NZ	507534	A	01-02-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/00773

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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